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Supplementary information

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Bispecific dual T cell agonist invikafusp alfa in solid tumors: the phase 1/2 START-001 trial

In the format provided by the authors and unedited

Bispecific dual T-cell agonist invikafusp alfa in immune checkpoint blockade-resistant, antigen-rich solid tumors: the phase 1/2 START-001 trial

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Supplementary Table 1 | Frequency and severity of treatment-related adverse events (preferred term) occurring in all phase 1 participants (%, n/N)

Dose level (mg/kg) and N	0.01 N=3				0.02 N=4				0.04 N=4				0.08 N=13				0.12 N=7				0.16 N=3			
Grade / Preferred term	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Cytokine release syndrome	33.3 (1/3)	66.7 (2/3)	0	0	50.0 (2/4)	0	50.0 (2/4)	0	25.0 (1/4)	75.0 (3/4)	0	0	38.5 (5/13)	46.2 (6/13)	15.4 (2/13)	0	14.3 (1/7)	71.4 (5/7)	0	0	0	66.7 (2/3)	33.3 (1/3)	0
Nausea	66.7 (2/3)	0	0	0	0	0	0	0	0	0	0	0	61.5 (8/13)	7.7 (1/13)	0	0	14.3 (1/7)	14.3 (1/7)	14.3 (1/7)	0	66.7 (2/3)	0	0	0
Pruritus	0	0	0	0	0	0	0	0	25.0 (1/4)	0	0	0	30.8 (4/13)	30.8 (4/13)	15.4 (2/13)	0	14.3 (1/7)	28.6 (2/7)	14.3 (1/7)	0	66.7 (2/3)	33.3 (1/3)	0	0
Rash	0	66.7 (2/3)	0	0	25.0 (1/4)	25.0 (1/4)	0	0	25.0 (1/4)	0	0	0	7.7 (1/13)	23.1 (3/13)	0	0	28.6 (2/7)	28.6 (2/7)	14.3 (1/7)	0	33.3 (1/3)	0	33.3 (1/3)	0
Vomiting	0	66.7 (2/3)	0	0	0	0	0	0	0	0	0	0	15.4 (2/13)	23.1 (3/13)	0	0	42.9 (3/7)	28.6 (2/7)	0	0	33.3 (1/3)	0	0	0
Chills	66.7 (2/3)	33.3 (1/3)	0	0	0	0	0	0	0	25.0 (1/4)	0	0	30.8 (4/13)	46.2 (6/13)	0	0	0	0	0	0	0	0	0	0
Platelet count decreased	33.3 (1/3)	0	33.3 (1/3)	0	0	25.0 (1/4)	0	0	0	0	0	0	15.4 (2/13)	15.4 (2/13)	7.7 (1/13)	0	0	14.3 (1/7)	28.6 (2/7)	0	33.3 (1/3)	0	0	0
Alanine aminotransferase increased	0	0	0	0	25.0 (1/4)	25.0 (1/4)	0	0	0	0	0	0	15.4 (2/13)	23.1 (3/13)	0	0	14.3 (1/7)	14.3 (1/7)	0	0	33.3 (1/3)	0	0	0
Infusion related reaction	0	0	0	0	0	25.0 (1/4)	0	0	0	75.0 (3/4)	0	0	7.7 (1/13)	23.1 (3/13)	0	0	14.3 (1/7)	42.9 (3/7)	0	0	0	33.3 (1/3)	0	0
Aspartate aminotransferase increased	0	0	0	0	0	25.0 (1/4)	25.0 (1/4))	0	0	0	0	0	15.4 (2/13)	7.7 (1/13)	0	0	14.3 (1/7)	14.3 (1/7)	0	0	33.3 (1/3)	0	0	0
Eosinophil count increased	66.7 (2/3)	0	0	0	75.0 (3/4)	0	0	0	0	0	0	0	30.8 (4/13)	0	0	0	14.3 (1/7)	0	0	0	0	0	0	0

Dose level (mg/kg) and N	0.01 N=3				0.02 N=4				0.04 N=4				0.08 N=13				0.12 N=7				0.16 N=3			
Grade / Preferred term	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Lymphocyte count decreased	0	0	33.3 (1/3)	33.3 (1/3)	0	0	0	50.0 (2/4)	0	0	0	0	0	0	0	23.1 (3/13)	0	0	0	14.3 (1/7)	0	0	0	33.3 (1/3)
Sinus tachycardia	0	0	0	0	0	0	0	0	25.0 (1/4)	50.0 (2/4)	0	0	7.7 (1/13)	0	0	0	14.3 (1/7)	0	14.3 (1/7)	0	33.3 (1/3)	0	0	0
Tachycardia	0	33.3 (1/3)	0	0	0	50.0 (2/4)	0	0	0	0	0	0	7.7 (1/13)	7.7 (1/13)	0	0	14.3 (1/7)	14.3 (1/7)	0	0	0	0	0	0
Blood bilirubin increased	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	15.4 (2/13)	0	0	28.6 (2/7)	0	0	0	0	33.3 (1/3)	0
Hypocalcaemia	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	7.7 (1/13)	7.7 (1/13)	7.7 (1/13)	0	0	14.3 (1/7)	0	0	0	33.3 (1/3)	0	0
Oedema peripheral	33.3 (1/3)	0	0	0	0	0	0	0	0	0	0	0	15.4 (2/13)	0	0	0	14.3 (1/7)	14.3 (1/7)	0	0	66.7 (2/3)	0	0	0
Stomatitis	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	7.7 (1/13)	15.4 (2/13)	0	0	14.3 (1/7)	14.3 (1/7)	0	0	0	0	0	0
Arthralgia	0	0	0	0	50.0 (2/4)	0	0	0	0	0	0	0	0	7.7 (1/13)	7.7 (1/13)	0	14.3 (1/7)	14.3 (1/7)	0	0	0	0	0	0
Diarrhoea	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	28.6 (2/7)	0	0	0	0	0	0	0
Hypomagnesaemia	0	0	0	0	0	0	0	0	0	0	0	0	23.1 (3/13)	0	0	0	0	14.3 (1/7)	0	0	33.3 (1/3)	0	0	0
Pyrexia (not related to CRS)	33.3 (1/3)	0	0	0	0	0	0	0	0	0	0	0	15.4 (2/13)	15.4 (2/13)	0	0	14.3 (1/7)	0	0	0	0	0	0	0
Fatigue	0	0	0	0	0	0	0	0	0	0	0	0	15.4 (2/13)	0	0	0	28.6 (2/7)	14.3 (1/7)	0	0	33.3 (1/3)	0	0	0
Gamma-glutamyltransferase increased	0	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	7.7 (1/13)	0	0	14.3 (1/7)	0	0	0	33.3 (1/3)	0	0	0
Hypoalbuminaemia	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	28.6 (2/7)	0	0	33.3 (1/3)	0	0	0
Decreased appetite	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	28.6 (2/7)	0	0	0	0	0	0	0
Hypophosphataemia	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	7.7 (1/13)	0	0	0	14.3 (1/7)	0	0	0	33.3 (1/3)	0	0
Anaemia	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	28.6 (2/7)	0	0	0	0	0	0

Dose level (mg/kg) and N	0.01 N=3				0.02 N=4				0.04 N=4				0.08 N=13				0.12 N=7				0.16 N=3			
Grade / Preferred term	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Arthritis	0	0	0	0	0	0	0	0	0	0	0	0	0	15.4 (2/13)	0	0	14.3 (1/7)	0	0	0	0	0	0	0
Blood alkaline phosphatase increased	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	7.7 (1/13)	7.7 (1/13)	0	0	0	0	0	0	0	0	0
Dry mouth	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	28.6 (2/7)	0	0	0	0	0	0	0
Flushing	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Hypotension (only not related to CRS)	33.3 (1/3)	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Myalgia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0
Neutrophil count decreased	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	15.4 (2/13)	0	0	0	0	0	0	33.3 (1/3)	0	0
Dry skin	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0
Dyspepsia	0	0	0	0	0	0	0	0	0	0	0	0	0	23.1 (3/13)	0	0	0	0	0	0	0	0	0	0
Dyspnoea	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Headache	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	7.7 (1/13)	0	0	0	0	0	0	33.3 (1/3)	0	0	0
Hyponatraemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	33.3 (1/3)	0	0	0
Neutropenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Acute kidney injury	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Ascites	0	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	14.3 (1/7)	0	0	0	0	0
Blood albumin decreased	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Confusional state	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Dose level (mg/kg) and N	0.01 N=3				0.02 N=4				0.04 N=4				0.08 N=13				0.12 N=7				0.16 N=3			
Grade / Preferred term	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Cough	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Dizziness	33.3 (1/3)	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Dysphagia	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	33.3 (1/3)	0	0	0
Hyperbilirubinaemia	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Hypersensitivity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	33.3 (1/3)	0	0
Hypothyroidism	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	(28.6 (2/7)	0	0	0	0	0	0
Muscular weakness	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0
Protein urine	0	0	0	0	0	0	0	0	0	0	0	0	15.4 (2/13)	0	0	0	0	0	0	0	0	0	0	0
Tumour pain	0	33.3 (1/3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urine analysis abnormal	0	0	0	0	0	0	0	0	0	0	0	0	15.4 (2/13)	0	0	0	0	0	0	0	0	0	0	0
White blood cell count decreased	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0
Abdominal pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Aspartate aminotransferase	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Asthenia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Back pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bilirubin conjugated increased	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Blood creatine phosphokinase increased	0	0	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Dose level (mg/kg) and N	0.01 N=3				0.02 N=4				0.04 N=4				0.08 N=13				0.12 N=7				0.16 N=3			
Grade / Preferred term	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Blood creatinine increased	0	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Bronchial obstruction	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0
Capillary leak syndrome	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Dermatitis exfoliative	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Drug eruption	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0
Dysgeusia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Dyspnoea exertional	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Eczema	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0
Erythema	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Face oedema	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gastrooesophageal reflux disease	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0	0
Generalised oedema	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Glossodynia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0	0
Hyperglycaemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperthyroidism	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hyperuricaemia	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hypokalaemia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0
Influenza like illness	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	33.3 (1/3)	0	0	0
Lung opacity	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Dose level (mg/kg) and N	0.01 N=3				0.02 N=4				0.04 N=4				0.08 N=13				0.12 N=7				0.16 N=3			
Grade / Preferred term	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Malaise	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Neck pain	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Neuralgia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Non-cardiac chest pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Oral pain	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Oropharyngeal pain	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0
Pain in extremity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	0	0	0	0	25.0 (1/4)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Paraesthesia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Pharyngeal paraesthesia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0	0
Pleural effusion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Psoriasis	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Red blood cells urine	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Skin disorder	0	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0
Skin exfoliation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Skin ulcer	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0	0	0	0
Syncope	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14.3 (1/7)	0	0	0	0
Tremor	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Uncoded	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0

Dose level (mg/kg) and N	0.01 N=3				0.02 N=4				0.04 N=4				0.08 N=13				0.12 N=7				0.16 N=3			
Grade / Preferred term	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Ventricular tachycardia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Weight increased	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0
Wheezing	33.3 (1/3)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
White blood cells urine	0	0	0	0	0	0	0	0	0	0	0	0	7.7 (1/13)	0	0	0	0	0	0	0	0	0	0	0

Supplementary Table 2 I Frequency and severity of treatment-related adverse events (preferred term) occurring in all participants (initial phase 2 and total) (%, n/N)

Phase and N	Initial phase 2 N=18				Total (phase 1 + initial phase 2) N=52			
Grade / Preferred Term	1	2	3	4	1	2	3	4
Cytokine release syndrome	11.1 (2/18)	44.4 (8/18)	16.7 (3/18)	0	23.1 (12/52)	50.0 (26/52)	15.4 (8/52)	0
Nausea	33.3 (6/18)	16.7 (3/18)	0	0	36.5 (19/52)	9.6 (5/52)	1.9 (1/52)	0
Pruritus	27.8 (5/18)	11.1 (2/18)	0	0	25.0 (13/52)	17.3 (9/52)	5.8 (3/52)	0
Rash	5.6 (1/18)	38.9 (7/18)	5.6 (1/18)	0	13.5 (7/52)	28.8 (15/52)	5.8 (3/52)	0
Vomiting	5.6 (1/18)	33.3 (6/18))	0	0	13.5 (7/52)	25.0 (13/52)	0	0
Chills	11.1 (2/18)	16.7 (3/18)	0	0	15.4 (8/52)	21.2 (11/52)	0	0
Platelet count decreased	5.6 (1/18)	16.7 (3/18)	16.7 (3/18)	0	9.6 (5/52)	13.5 (7/52)	13.5 (7/52)	0
Alanine aminotransferase increased	16.7 (3/18)	5.6 (1/18)	5.6 (1/18)	0	15.4 (8/52)	11.5 (6/52)	1.9 (1/52)	0
Infusion related reaction	0	5.6 (1/18)	0	0	3.8 (2/52)	23.1 (12/52)	0	0
Aspartate aminotransferase increased	16.7 (3/18)	0	11.1 (2/18)	0	13.5 (7/52)	5.8 (3/52)	5.8 (3/52)	0
Eosinophil count increased	5.6 (1/18)	0	0	0	21.2 (11/52)	0	0	0
Lymphocyte count decreased	0	0	0	11.1 (2/18)	0	0	1.9 (1/52)	19.2 (10/52)
Sinus tachycardia	11.1 (2/18)	5.6 (1/18)	0	0	11.5 (6/52)	5.8 (3/52)	1.9 (1/52)	0
Tachycardia	11.1 (2/18)	5.6 (1/18)	0	0	7.7 (4/52)	11.5 (6/52)	0	0

Phase and N	Initial phase 2 N=18				Total (phase 1 + initial phase 2) N=52			
Grade / Preferred Term	1	2	3	4	1	2	3	4
Blood bilirubin increased	11.1 (2/18)	0	5.6 (1/18)	0	3.8 (2/52)	5.8 (3/52)	7.7 (4/52)	0
Hypocalcaemia	0	16.7 (3/18)	0	0	1.9 (1/52)	13.5 (7/52)	1.9 (1/52)	0
Oedema peripheral	5.6 (1/18)	5.6 (1/18)	0	0	13.5 (7/52)	3.8 (2/52)	0	0
Stomatitis	11.1 (2/18)	0	0	0	7.7 (4/52)	7.7 (4/52)	0	0
Arthralgia	0	0	5.6 (1/18)	0	5.8 (3/52)	3.8 (2/52)	3.8 (2/52)	0
Diarrhoea	16.7 (3/18)	0	5.6 (1/18)	0	11.5 (6/52)	0	1.9 (1/52)	0
Hypomagnesaemia	5.6 (1/18)	5.6 (1/18)	0	0	9.6 (5/52)	3.8 (2/52)	0	0
Pyrexia (not related to CRS)	5.6 (1/18)	0	0	0	9.6 (5/52)	3.8 (2/52)	0	0
Fatigue	0	0	0	0	9.6 (5/52)	1.9 (1/52)	0	0
Gamma-glutamyltransferase increased	0	5.6 (1/18)	5.6 (1/18)	0	3.8 (2/52)	3.8 (2/52)	3.8 (2/52)	0
Hypoalbuminaemia	5.6 (1/18)	5.6 (1/18)	0	0	3.8 (2/52)	7.7 (4/52)	0	0
Decreased appetite	5.6 (1/18)	5.6 (1/18)	0	0	3.8 (2/52)	3.8 (2/52)	0	0
Hypophosphataemia	5.6 (1/18)	0	0	0	3.8 (2/52)	3.8 (2/52)	0	0
Anaemia	0	0	0	0	0	3.8 (2/52)	1.9 (1/52)	0
Arthritis	0	5.6 (1/18)	0	0	1.9 (1/52)	3.8 (2/52)	0	0
Blood alkaline phosphatase increased	5.6 (1/18)	0	0	0	3.8 (2/52)	1.9 (1/52)	1.9 (1/52)	0
Dry mouth	5.6 (1/18)	0	0	0	7.7 (4/52)	0	0	0
Flushing	5.6 (1/18)	5.6 (1/18)	0	0	3.8 (2/52)	3.8 (2/52)	0	0
Hypotension (only count those not related CRS,	0	11.1 (2/18)	0	0	1.9 (1/52)	3.8 (2/52)	0	0

Phase and N	Initial phase 2 N=18				Total (phase 1 + initial phase 2) N=52			
Grade / Preferred Term	1	2	3	4	1	2	3	4
exclude those related to CRS)								
Myalgia	5.6 (1/18)	11.1 (2/18)	0	0	1.9 (1/52)	3.8 (2/52)	0	0
Neutrophil count decreased	0	0	0	0	0	3.8 (2/52)	3.8 (2/52)	0
Dry skin	11.1 (2/18)	0	0	0	3.8 (2/52)	1.9 (1/52)	0	0
Dyspepsia	0	0	0	0	0	3.8 (2/52)	0	0
Dyspnoea	0	11.1 (2/18)	0	0	1.9 (1/52)	3.8 (2/52)	0	0
Headache	0	0	0	0	3.8 (2/52)	1.9 (1/52)	0	0
Hyponatraemia	5.6 (1/18)	0	5.6 (1/18)	0	3.8 (2/52)	0	1.9 (1/52)	0
Neutropenia	0	16.7 (3/18)	0	0	0	3.8 (2/52)	0	0
Acute kidney injury	0	0	5.6 (1/18)	0	1.9 (1/52)	0	1.9 (1/52)	0
Ascites	0	0	0	0	0	0	3.8 (2/52)	0
Blood albumin decreased	0	0	0	0	1.9 (1/52)	1.9 (1/52)	0	0
Confusional state	5.6 (1/18)	0	0	0	1.9 (1/52)	1.9 (1/52)	0	0
Cough	5.6 (1/18)	0	0	0	1.9 (1/52)	1.9 (1/52)	0	0
Dizziness	0	0	0	0	3.8 (2/52)	0	0	0
Dysphagia	0	0	0	0	3.8 (2/52)	0	0	0
Hyperbilirubinaemia	0	0	0	0	1.9 (1/52)	1.9 (1/52)	0	0
Hypersensitivity	0	0	0	0	0	3.8 (2/52)	0	0
Hypothyroidism	0	0	0	0	0	3.8 (2/52)	0	0
Muscular weakness	0	5.6 (1/18)	0	0	0	3.8 (2/52)	0	0
Protein urine	0	0	0	0	3.8 (2/52)	0	0	0
Tumour pain	0	5.6 (1/18)	0	0	0	3.8 (2/52)	0	0
Urine analysis abnormal	0	0	0	0	3.8 (2/52)	0	0	0

Phase and N	Initial phase 2 N=18				Total (phase 1 + initial phase 2) N=52			
Grade / Preferred Term	1	2	3	4	1	2	3	4
White blood cell count decreased	0	0	0	0	1.9 (1/52)	0	1.9 (1/52)	0
Abdominal pain	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Aspartate aminotransferase	0	0	0	0	0	1.9 (1/52)	0	0
Asthenia	0	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0
Back pain	0	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0
Bilirubin conjugated increased	0	0	0	0	0	1.9 (1/52)	0	0
Blood creatine phosphokinase increased	0	0	0	0	0	0	0	1.9 (1/52)
Blood creatinine increased	0	0	0	0	0	0	1.9 (1/52)	0
Bronchial obstruction	0	0	0	0	0	1.9 (1/52)	0	0
Capillary leak syndrome	0	0	0	0	0	1.9 (1/52)	0	0
Dermatitis exfoliative	0	0	0	0	0	1.9 (1/52)	0	0
Drug eruption	0	0	0	0	0	1.9 (1/52)	0	0
Dysgeusia	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Dyspnoea exertional	0	0	0	0	0	1.9 (1/52)	0	0
Eczema	0	0	0	0	0	1.9 (1/52)	0	0
Erythema	0	0	0	0	1.9 (1/52)	0	0	0
Face oedema	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Gastrooesophageal reflux disease	0	0	0	0	1.9 (1/52)	0	0	0
Generalised oedema	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Glossodynia	0	0	0	0	1.9 (1/52)	0	0	0

Phase and N	Initial phase 2 N=18				Total (phase 1 + initial phase 2) N=52			
Grade / Preferred Term	1	2	3	4	1	2	3	4
Hyperglycaemia	0	0	5.6 (1/18)	0	0	0	1.9 (1/52)	0
Hyperthyroidism	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Hyperuricaemia	0	0	0	0	1.9 (1/52)	0	0	0
Hypokalaemia	0	0	0	0	0	1.9 (1/52)	0	0
Influenza like illness	0	0	0	0	1.9 (1/52)	0	0	0
Lung opacity	0	0	0	0	1.9 (1/52)	0	0	0
Malaise	0	0	0	0	1.9 (1/52)	0	0	0
Neck pain	0	0	0	0	1.9 (1/52)	0	0	0
Neuralgia	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Non-cardiac chest pain	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Oral pain	0	0	0	0	1.9 (1/52)	0	0	0
Oropharyngeal pain	0	0	0	0	0	1.9 (1/52)	0	0
Pain in extremity	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Palmar-plantar erythrodysaesthesia syndrome	0	0	0	0	1.9 (1/52)	0	0	0
Paraesthesia	0	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0
Pharyngeal paraesthesia	0	0	0	0	1.9 (1/52)	0	0	0
Pleural effusion	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Psoriasis	0	0	0	0	1.9 (1/52)	0	0	0
Red blood cells urine	0	0	0	0	1.9 (1/52)	0	0	0
Skin disorder	0	0	0	0	0	1.9 (1/52)	0	0
Skin exfoliation	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0	0
Skin ulcer	0	0	0	0	1.9 (1/52)	0	0	0
Syncope	0	0	0	0	0	0	0	1.9 (1/52)

Phase and N	Initial phase 2 N=18				Total (phase 1 + initial phase 2) N=52			
Grade / Preferred Term	1	2	3	4	1	2	3	4
Tremor	0	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0
Uncoded	0	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0
Urticaria	0	0	0	0	1.9 (1/52)	0	0	0
Ventricular tachycardia	0	5.6 (1/18)	0	0	0	1.9 (1/52)	0	0
Weight increased	0	0	0	0	1.9 (1/52)	0	0	0
Wheezing	0	0	0	0	1.9 (1/52)	0	0	0
White blood cells urine	0	0	0	0	1.9 (1/52)	0	0	0

Supplementary Table 3 | Frequency and severity of cytokine-release syndrome (CRS) after invika treatment (Group A* vs. Group B[+]) (%, n/N)

Grade[#]	1		2		3		4		5		Total	
Group and N	A (N=7)	B (N=6)	A (N=7)	B (N=6)	A (N=7)	B (N=6)	A (N=7)	B (N=6)	A (N=7)	B (N=6)	A (N=7)	B (N=6)
CRS	14.3 (1/7)	16.7 (1/6)	71.4 (5/7)	66.7 (4/6)	0	0	0	0	0	0	85.7 (6/7)	83.3 (5/6)

[*] Group A (0.12 mg/kg without step-up dosing); [+]Group B (Step-up dosing [0.01/0.02/0.12 mg/kg]); [#]Graded per American Society for Transplantation and Cellular Therapy consensus grading for CRS and ICANS.

Supplementary Table 4 | T/B/NK and TCRvβ6/10 flow panel markers and fluorochromes

Laser	Detector	Fluorochrome	Marker	Vendor	Catalog #	Clone	Vol/Test µL (per 1e6 cells in 100 µL)
Violet 407 nm	V450	BV421	CD25	BioLegend	356114	M-A251	5.00
	V525	Zombie Aqua	Viability	BioLegend	423104	N/A	1:200
	V610	BV605	CD8	BioLegend	301040	RPA-T8	5.00
Blue 488nm	B530	Alexa Fluor488	CD3	BioLegend	300415	UCHT1	2.00
	B695	PE	CD56	BD Biosciences	340363	NCAM16.2	2.50
	B530	PerCP-Cy5.5	CD4	BD Biosciences	552838	L200	2.50
	B695	PE-Cy7	CD45	BioLegend	304016	HI30	2.00
Red 633nm	R670	APC	TCRvβ6/10	Marengo	Custom	N/A	100 nM
	R730	Alexa Fluor700	CD14	BioLegend	301822	M5E2	2.50
	R780	APC-Fire750	CD20	BioLegend	302358	2H7	2.50

T/B/NK and TCRvβ6/10 Flow Panel (10-color): Live/Dead Viability dye, CD3, CD4, CD8, CD14, CD20, CD25, CD45, CD56 and TCRvβ6/10.

Supplementary Table 5 | Cell Populations Reported for the T/B/NK and TCRvβ6/10 flow panel assay

Populations	CD45	CD14	CD20	CD3	CD56	CD4	CD8	CD25	TCVvβ	Cell type	Gating hierarchy
CD14+ Monocytes	+	+								Monocytes	Time/FSG/SSG/CD45+/Live/CD14+ | Freq. of Parent
CD20+ B cells	+	-	+							B cells	Time/FSG/SSG/CD45+/Live/CD14-/CD20+ | Freq. of Parent
CD56 Total NK cells	+	-	-		+					NK cells	Time/FSG/SSG/CD45+/Live/CD14-/CD20-/NK Total | Freq. of Parent
CD56++ NK cells	+	-	-		++						Time/FSG/SSG/CD45+/Live/CD14-/CD20-/NKbright | Freq. of Parent
CD3+ T cells	+	-	-	+	-					CD3+ T cells	Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+ | Freq. of Parent
CD3+ T cells (%FoGP)	+	-	-	+	-						Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+ | Freq. of CD14-
CD3+ TCRvB+	+	-	-	+	-				+		Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+/TCRvB+ | Freq. of Parent
CD3+ TCRvB+ CD25+	+	-	-	+	-			+	+		Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+/TCRvB+/CD25+ | Freq. of Parent
CD4+ T cells	+	-	-	+	-	+	-			CD4+ T cells	Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+/CD4+CD8- | Freq. of Parent
CD4+ TCRvB+	+	-	-	+	-	+	-		+		Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+/CD4+CD8-/TCRvB+ | Freq. of Parent
CD4+ TCRvB+ CD25+	+	-	-	+	-	+	-	+	+		Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+/CD4+CD8-/TCRvB+/CD25+ | Freq. of Parent

Populations	CD45	CD14	CD20	CD3	CD56	CD4	CD8	CD25	TCVvβ	Cell type	Gating hierarchy
CD8+ T cells	+	-	-	+	-	-	+			CD8+ T cells	Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+/CD4- CD8+ | Freq. of Parent
CD8+ TCRvB+	+	-	-	+	-	-	+		+		Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+/CD4- CD8+/TCRvB+ | Freq. of Parent
CD8+ TCRvB+ CD25+	+	-	-	+	-	-	+	+	+		Time/FSG/SSG/CD45+/Live/CD14-/CD20-/CD56-/CD3+/CD4- CD8+/TCRvB+/CD25+ | Freq. of Parent

The annotation '+' is used to represent positive cells, for example CD4+ T cells, means all cells that are positive for CD4. The annotation '-' is used to represent negative cells, for example CD14-, means all cells that are negative for CD14. The annotation '++' is used to represent brightly expressed positive cells.

Abbreviations: CD, cluster of differentiation; FoGP, frequency of grandparent; Freq., frequency; FSG, forward scatter gate; NK, natural killer; SSG, side scatter gate; TCRvβ (TCRVβ/TCRvB), T-cell receptor variable β chain.

Supplementary Table 6 | List of materials

Description	Vendor	Lot
AllPrep DNA/RNA FFPE Kit	Qiagen	172042887
RNeasy Mini Kit	Qiagen	56902312
MagMAX for Stabilized Blood Tube RNA Isolation	Thermo	4451894
Qubit RNA HS Assay	Thermo	2295063
Agilent RNA 6000 Nano kit	Agilent	AQ23BK20
Human CAR-T Panel	NanoString	RC9839X1 CP9839X1
Human CAR-T Panel Standard	NanoString	T20210712-2
nCounter Cartridge	NanoString	31021013581
nCounter Prep Plate	NanoString	41021170-0247
nCounter Master kit	NanoString	230223

Supplementary Table 7 | List of antibodies

Reagents	Vendor	Cat #	Lot #	Concentration
Anti-CD20 antibody [EP459Y]	Abcam	ab78237	1006245-2	0.056 mg/mL
CD8α (C8/144B) Mouse mAb (IHC Specific)	Cell Signaling	70306S	4	25 µg/mL
CD3ε (D7A6E™) XP® Rabbit mAb	Cell Signaling	85061S	5	76 µg/mL
NCAM (CD56) (123C3) Mouse mAb #3576	Cell Signaling	3576S	9	559 µg/mL
CD14 (D7A2T) Rabbit mAb (IHC Formulated) #75181	Cell Signaling	75181S	1	5 µg/mL
Recombinant Anti-CD4 antibody [EPR6855] (ab133616)	Abcam	ab133616	1008803-3	0.143 mg/mL
Recombinant Anti-IL-2 Receptor alpha antibody [EPR6452]	Abcam	ab128955	GR280865-14	1.999 mg/mL
CD45 Monoclonal Antibody (CD45-2B11), Biotin, eBioscience™	Thermo Fisher	13-9457-82	2527221	0.5 mg/mL
CD3 epsilon Antibody (C3e/1931) [Biotin]	Novus Biologicals	NBP2-79840B	D123361	1.28 mg/mL
Rabbit (DA1E) mAb IgG XP® Isotype Control #3900	Cell Signaling	3900	48	2.5 mg/mL
Mouse (G3A1) mAb IgG1 Isotype Control #5415	Cell Signaling	5415	13	2.5 mg/mL
Human IgG Isotype Control [Biotin]	Novus Biologicals	NBP1-96855	SEP2022	1 mg/mL

Abbreviations: Cat #, catalog number; CD, cluster of differentiation; IgG, immunoglobulin G; IHC, immunohistochemistry; IL-2, interleukin-2; Lot #, lot number; mAb, monoclonal antibody; NCAM, neural cell adhesion molecule.

Supplementary Table 8 | Management of invikafusp infusion-related reactions

NCI CTCAE grade	Treatment	Premedication at subsequent dosing
Grade 1: Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator.	None
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDS • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.	Participant may be premedicated 30-45 minutes prior to infusion of invikafusp with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic).

Grades 3 or 4 **Grade 3:** Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor, or ventilatory support indicated	Stop infusion. Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Vasopressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. Discuss with the Sponsor regarding further trial treatment administration.	No subsequent dosing

Abbreviations: NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; IV, intravenous; NSAID, nonsteroidal anti-inflammatory drug; PO, “per os” (by mouth [DW).

Supplementary Table 9 | Definition of dose-limiting toxicity (DLT)

DLT definition	DLT exceptions
A DLT is defined as any of the following AEs occurring during the DLT Evaluation Period of Cycle 1, which are possibly, probably, or definitely related to the investigational drug and will include: • Any death not clearly due to the underlying disease or extraneous causes • Any toxicity that results in a >28-day treatment delay • Non-hematologic toxicity: – Any toxicity ≥ Grade 3 with the exceptions as noted in DLT exceptions below: – Hy's law cases ○ AST and/or ALT >3 × ULN ○ Concurrent elevation of total bilirubin >2 × ULN ○ No alternative etiology can be identified • Hematologic toxicity: – Grade 4 lymphopenia, neutropenia or thrombocytopenia lasting >7 days (transient peripheral lymphopenia is expected per the mechanism of action of invikafusp) – Grade ≥3 neutropenia associated with complications secondary to infection and neutropenic fever lasting >48 hours – Grade 3 thrombocytopenia with clinically significant bleeding	• Grade 3 electrolyte abnormality lasting <72 hours, without associated clinical complications, and responding to therapy; • Grade 3 fever lasting <72 hours and not associated with hemodynamic instability • Grade 3 nausea or vomiting resolving to Grade ≤1 within 72 hours with or without medical intervention • Grade 3 diarrhea, constipation or abdominal pain resolving to Grade ≤1 within 72 hours with or without medical therapy • Grade 3 fatigue resolving to Grade 1 within <7 days • Grade 3 CRS/infusion reaction improving to ≤ Grade 2 within 72 hours and responding to medical intervention. Grading is based on overall CRS/infusion reaction event, and not grade of individual signs or symptoms including fever, chills, nausea or vomiting, diarrhea, hypotension, hypertension, or tachycardia • Grade 3 skin toxicity resolving to Grade ≤2 within 7 days of initiation of oral corticosteroids • Grade 3 inflammatory reaction secondary to anti-tumor response such as rash and lymph node pain resolving to Grade ≤1 within 7 days; • Grade 3 AST and/or ALT elevation returned to Grade 1 or baseline within 7 days • Grade 4 laboratory abnormalities that are not considered clinically relevant, and improved to Grade ≤2 within 7 days

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRS, cytokine release syndrome; DLT, dose-limiting toxicity; ULN, upper limit normal.

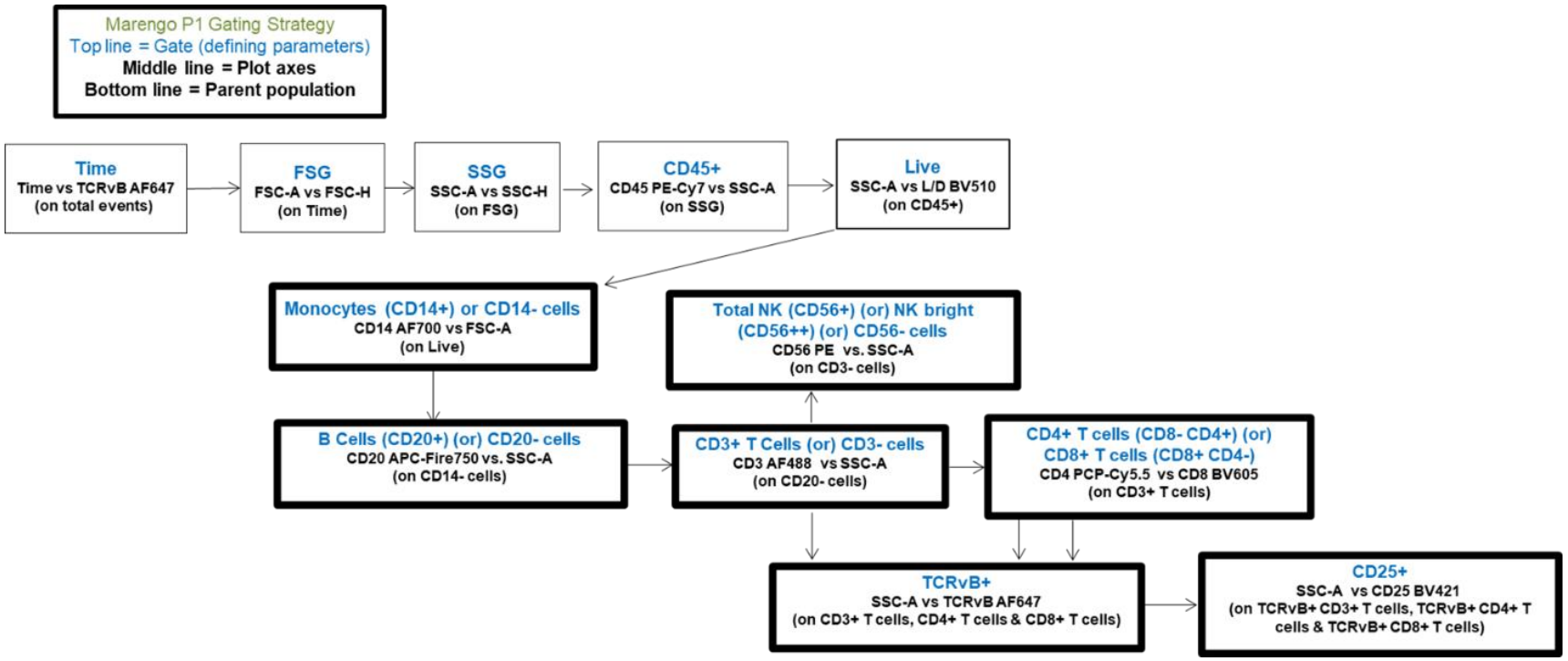
Supplementary Table 10 | Summary of all protocol amendments and rationale for changes

Version	Version Date	Comments	Major Change(s) and Rationale for the Change
1.0	10 Aug 2022	Original IND protocol	Not Applicable (N/A)
1.01	12 Sept 2022	Incorporating FDA review comments (non-hold), submitted to FDA only.	Not Applicable (N/A)
1.02	16 Sept 2022	After IND in effect, administrative and format changes, submitted to IRBs. No Summary of Changes	Not Applicable (N/A)
2.0	25 Jan 2023	Submitted to FDA and IRBs.	Change of trial design to a conventional 3 + 3 dose escalation and removal of the accelerated titration using a single subject for Dose Levels 1 and 2. The rationale for this change was to follow the FDA guidance that if a Grade 2 or above occurred in Dose Level 1 or Dose Level 2, the corresponding and subsequent dose levels needed to be converted to 3 + 3 design. The first patient of Dose Level 1 experienced a transient Grade 2 event (low blood pressure) corrected by intravenous fluid bolus, hence the trial design was revised to be 3+3 at Dose Level 1 and all subsequent dose levels per pre-specification.
2.01	03 May 2023	Administrative and format changes. Submitted to FDA, IRBs, and Health Canada. This was the version for HC initial CTA approval.	Not Applicable (N/A)

Version	Version Date	Comments	Major Change(s) and Rationale for the Change
3.0	27 June 2023	Submitted to FDA, Health Canada, IRBs, and first submission to EMA (CTIS) for initial EU CTA approval.	Addition of Phase 1 Group B, a step-up dosing (SUD) prior to dose escalation based on a modified BOIN (mBOIN) design. The rationale for this addition was to support further STAR0602 dose escalation and further maximize the potential for clinical activity while mitigating the risk of early post-infusion adverse effects to subjects. In addition, adding Phase 1 Group B with SUD was part of our dosage optimization strategy per FDA dosage optimization guidance.
3.01ANSM	20 Mar 2024	Re-submitted to EMA CTIS post review and requirement by French Agency (ANSM, reporting member state) for protocol revision	Modified eligibility criteria to change ECOG performance to 0 or 1 (not including 2) per ANSM requirement. Added two non-laboratory Grade 4 events related to the study drug as one of the study stopping criteria per ANSM requirement.
4.0	08 August 2024	Submitted to FDA, Health Canada, EU and IRBs.	This amendment was to formally close the Phase 1 dose escalation after the safety review committee (SRC) thoroughly reviewed all Phase 1 data (clinical pharmacology, safety and anti-tumor activity). Based on its review, SRC recommended a recommended Phase 2 dose (RP2D) of 0.08 mg/kg Q2W without step-up dosing and activation of the Phase 2 portions of the trial. In addition, this amendment incorporated initial dosage optimization per FDA guidance by adding Q3W, Q6W dosing schedules.
5.0	18 May 2026	Current version, submitted to FDA, Health Canada, EU and IRBs.	Added Cohort 10 (microsatellite stable, metastatic colorectal cancer) using invikafusp alfa in combination with standard single-agent irinotecan as second-line therapy Revised Cohort 8 (metastatic non-small cell lung cancer) using invikafusp alfa in combination with standard single-agent docetaxel as second-line therapy. Rationale for these two cohorts was based on the preliminary tumor responses seen in invikafusp monotherapy in these indications and the preliminary

Version	Version Date	Comments	Major Change(s) and Rationale for the Change
			tumor responses seen in the metastatic breast cancer patients who received invikafusp in combination with sacituzumab (a trop-2 targeting antibody drug conjugate). It was also based on the potential additive or synergistic MoA between chemotherapy which can induce immunogenic tumor cell death, releasing tumor antigen, and priming the immune system and invikafusp which could potentially activate such primed immune system better.

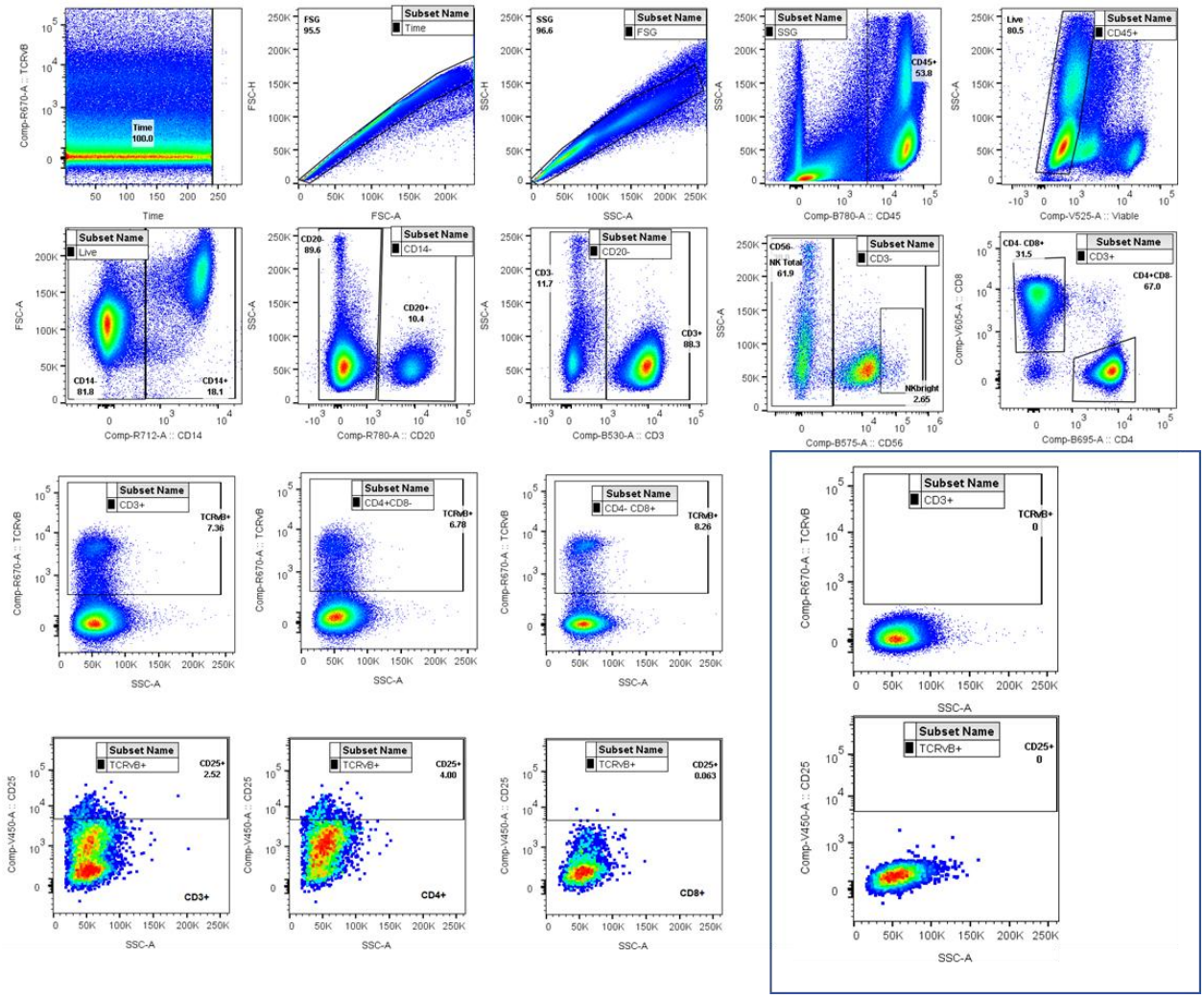
Supplementary Fig. 1 | Gating strategy for the T/B/NK and TCRvβ6/10 flow panel validation



Gating strategy utilized to represent the populations of interest listed in **Supplementary Table 5**.

Abbreviations: AF488, Alexa Fluor 488; AF647, Alexa Fluor 647; AF700, Alexa Fluor 700; APC-Fire750, allophycocyanin-Fire 750; BV421, Brilliant Violet 421; BV510, Brilliant Violet 510; BV605, Brilliant Violet 605; CD, cluster of differentiation; FSC-A, forward scatter area; FSC-H, forward scatter height; FSG, forward scatter gate; L/D, live/dead; NK, natural killer; PCP-Cy5.5 (PerCP-Cy5.5), peridinin-chlorophyll protein–cyanine 5.5; PE, phycoerythrin; PE-Cy7, phycoerythrin–cyanine 7; SSC-A, side scatter area; SSC-H, side scatter height; SSG, side scatter gate; TCRvβ (TCRVβ), T-cell receptor variable β chain.

Supplementary Fig. 2 | Representative flow panel scatter plots for gating the T cell/B cell/NK cell and TCRVβ immune populations of PBMCs



PBMCs (unstimulated) was obtained from a healthy human donor. The top row shows the time gate and gating of singlets, CD45+ leukocytes and live cells. The second row from the top shows the gating of monocytes, B cells, Total NK cells, NK bright cells, CD3+ T cells, CD4+ T cells and CD8+ T cells. The third row from the top shows the gating of TCRVβ+ cells, with the TCRVβ+ fluorescence minus one (FMO) plot represented on the right. The bottom row shows the gating of CD25+ cells, with the CD25 BV421 FMO plot represented on the right. Abbreviations: PBMCs, peripheral blood mononuclear cells; TCRVβ, T Cell Receptor variable region of beta chain.

Supplementary Information: Clinical Protocol



Clinical Study Protocol

Study Title:	A Phase 1/2, First-in-Human, Open-Label, Dose Escalation and Expansion Study of STAR0602, a Selective T Cell Receptor (TCR)-targeting, Bifunctional Antibody-fusion Molecule, in Subjects with Unresectable, Locally Advanced, or Metastatic Solid Tumors that are Antigen-rich (START-001)
Study Number:	CP-START-001
Protocol Version:	5.0
Study Phase:	Phase 1/2
Product Name:	STAR0602
IND Number:	179810
EU CT Number:	2023-505334-10-01
Indication:	Unresectable, locally advanced, or metastatic solid tumors
Investigators:	Multicenter
Sponsor:	Marengo Therapeutics, Inc
Sponsor Contact:	Can be found in the Investigator Trial File Binder (or equivalent)
Protocol Date:	18 May 2026

Confidentiality and Compliance Statements

All financial and nonfinancial support for this study will be provided by Marengo Therapeutics, Inc. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed, written consent of Marengo Therapeutics, Inc. The study will be conducted according to the International Council for Harmonisation harmonized tripartite guideline E6(R3): Good Clinical Practice.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	area under the curve
BOIN	Bayesian optimal interval
CDR	complementary-determining region
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
C_{max}	maximum concentration of drug
CNS	central nervous system
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CPI	checkpoint inhibitor
CR	complete response
CRC	colorectal cancer
CRS	cytokine release syndrome
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating cell-free tumor DNA
CTLA	cytotoxic T-lymphocyte-associated antigen
CV	coefficient of variation
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

DOR	duration of response
DPD	Data Protection Directive
EBV	Epstein-Barr Virus
EC_{50}	half maximal effective concentration
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
EEA	European Economic Area
eCRF	electronic case report form
EOI	end of infusion
EoT	End of Treatment
EoS	End of Study
EMR	Electronic Medical Record
FDA	Food and Drug Administration
FIH	first-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GGT	gamma glutamyl transpeptidase
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
HPV	human papilloma virus
HRT	hormone replacement therapy
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL-2	interleukin-2
IND	Investigational New Drug
irAE	immune-related adverse event
IRB	Institutional Review Board
iRECIST	immune RECIST

IV	Intravenous
MABEL	minimum anticipated biological effect level
mBOIN	modified Bayesian optimal interval
mCRPC	metastatic castration-resistant prostate cancer
MMR	mismatch repair
MoA	mechanism of action
MRI	magnetic resonance imaging
MSI	microsatellite instability
MSS	microsatellite stable
MTD	maximum tolerated dose
mTNBC	metastatic triple-negative breast cancer
NCI	National Cancer Institute
NHP	non-human primate
NK	natural killer
NOAEL	no observed adverse effect level
NOEL	no-effect limit
NSCLC	non-small cell lung cancer
OBD	optimal biological dose
ORR	overall response rate
OS	overall survival
PBL	peripheral blood lymphocytes
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	anti-programmed death 1
PD-L1	programmed death-ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PM	product monograph (Canada)
PR	partial response
PRO	patient-reported outcome

QW	once weekly
Q2W	every 2 weeks
Q3W	every 3 weeks
Q6W	every 6 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	Statistical Analysis Plan
sCD25	soluble CD25
SD	stable disease
SmPC	summary of product characteristics
SOI	start of infusion
SRC	Safety Review Committee
TCE	T cell engager
TCR	T cell receptor
TCRseq	TCR sequencing
TIL	tumor-infiltrating lymphocytes
TIME	tumor immune microenvironment
T_{max}	time to maximum plasma concentration
TMB-H	high-tumor mutational burden
TMB	tumor mutational burden
TMDD	target-mediated drug disposition
TNF	tumor necrosis factor
TRB	T cell receptor beta locus
iUPD	immune unconfirmed progressive disease
US	United States
USPI	United States prescribing information
USM	urgent safety measure
VAS	visual analog scale

Vβ	variable β
Vd	volume of distribution
Vss	Volume of distribution at steady state

1. SYNOPSIS

Protocol Number:	CP-START-001
Title:	A Phase 1/2, First-in-Human, Open-Label, Dose Escalation and Expansion Study of STAR0602, a Selective T Cell Receptor (TCR)-targeting, Bifunctional Antibody-fusion Molecule, in Subjects with Unresectable, Locally Advanced, or Metastatic Solid Tumors that are Antigen-rich (START-001)
Sponsor:	Marengo Therapeutics, Inc.
Study Phase:	Phase 1/2
Investigational Product:	STAR0602 is a bifunctional antibody-fusion molecule comprising an antibody Fab region (antibody arm) that binds to a subset of human αβ T cells expressing the germline-encoded variable beta 6 and 10 (Vβ6/Vβ10) chains of the T cell receptor (TCR) and a physiologically active, unmodified human IL-2 molecule (the other binding arm) fused to the IgG1 antibody Fc domain containing an N297A mutation to prevent interaction with Fc receptors. STAR0602 will be administered as an intravenous (IV) infusion over 30 to 60 minutes ± 5 minutes [starting doses will be administered over 60 minutes ± 5 minutes; infusion times to be revised based on safety and pharmacokinetic (PK) data during the study]. For Phase 2 Cohort 8 (primary stage 4 or recurrent NSCLC), commercially available docetaxel will be administered as an IV infusion over 60 ± 5 minutes as part of standard of care per United States Prescribing Information (USPI), Health Canada Product Monograph (PM) or EMA Summary of Product Characteristics (SmPC) in combination with STAR0602 for second-line therapy. For Phase 2 Cohort 10 [metastatic CRC with proficient DNA mismatch repair/microsatellite stable (mCRC with pMMR/MSS without TMB requirement)], commercially available irinotecan will be administered as an IV infusion over 90 ± 5 minutes as part of standard of care per USPI, PM or SmPC in combination with STAR0602 for second-line therapy.
Study Sites:	Up to 32 institutions in the United States (US), Canada and Europe experienced in the conduct of Phase 1/2 studies with cancer immunotherapy in participants with advanced cancer.
Study Rationale:	STAR0602 is a first-in-class T cell activator that selectively targets subsets of T cells expressing distinct germline-encoded Vβ chain variant TCRs that are enriched in tumor-infiltrating lymphocytes (TILs). STAR0602 potently expands naïve and antigen-specific T cells from healthy donors and cancer patients. In checkpoint inhibitor (CPI) therapy-refractory human and murine tumor models with a high tumor mutational burden, STAR0602 and its murine surrogate induced potent anti-tumor activity as monotherapy, including eradicating established tumors. This anti-tumor activity was mediated by selective expansion of targeted Vβ $CD8^+$ memory T cells. IV infusion of STAR0602 was generally well tolerated in cynomolgus monkeys over doses that induce significant expansion of activated Vβ6/Vβ10 $CD8^+$ T cells. Taken together, these data support the potential that STAR0602 might promote both

	potent and durable anti-tumor responses as a single agent in humans and provide a strong scientific rationale to investigate its potential effectiveness and safety in this Phase 1 /2 trial. In addition, STAR0602 in combination with standard chemotherapy may be beneficial. Chemotherapy can cause immunogenic death and potentiate the STAR0602 effect on T cell activation and proliferation which may potentially turn the immune "cold" tumors into a "hot" immune environment as suggested by pre-clinical studies. Therefore, such a combination could have additive/synergistic potential leading to improved responses and prolongation to PFS and OS, providing a strong rationale to investigate STAR0602 in combination with docetaxel in primary stage 4 or recurrent non-small cell lung cancer (NSCLC, Phase 2 Cohort 8) and irinotecan in mCRC with pMMR/MSS without TMB requirement (Phase 2 Cohort 10).
Indication:	For treatment of participants who have histologically confirmed solid tumors that are unresectable, locally advanced, or metastatic and for which standard curative therapies do not exist or are no longer effective.
Rationale for Trial Population:	Trial population includes: 1. Participants who have tumors with high tumor mutational burden (TMB-H) or microsatellite instability (MSI)-H/mismatch repair (MMR) deficient or virally associated ("immune hot tumors") for both Phase 1 and 2. • TMB has been shown to be a good enrichment/predictive biomarker for clinical response to checkpoint inhibitors (CPIs) and other immunotherapies, on the basis that tumors with TMB-H will likely present more neo-antigens and hence are more immunogenic for triggering a T cell response. For example, in the KEYNOTE158 study for participants receiving pembrolizumab and assessed for the association between antitumor activity and TMB, objective responses were observed in 30 of 102 participants (29%; 95% confidence interval [CI]: 21 – 39%) in the TMB-H group and 43 of 688 participants (6%; 95% CI: 5 – 8%) in the non-TMB-H group. • Tumors with MSI are deficient in deoxyribonucleic acid (DNA) MMR and consequently have a large mutational burden with presentation of large number of neoantigens. Clinical confirmation was derived from data from participants who were enrolled in 1 of 5 single-arm clinical trials. In 149 participants whose tumors harbored MSI, an overall response rate (ORR) of 39.6% (95% CI: 31.7 – 47.9%) had been shown with responses lasting 6 months or more for 78% of those who responded to pembrolizumab. There were 11 complete responses (CR) and 48 partial responses (PR). ORR was similar irrespective of whether participants had colorectal cancer (CRC) (36%) or a different cancer type (46% across the 14 other cancer types).

	• In an ex vivo human autologous TIL organoid model, the Sponsor showed that the STAR0602 had a strong anti-tumor activity against the TMB-H tumors. 2. Participants with "immune cold tumors" such as platinum-resistant epithelial ovarian cancer, metastatic microsatellite stable (MSS) CRC, and metastatic castration-resistant prostate cancer (mCRPC) to test whether STAR0602 could modulate the tumor immune microenvironment of these cancers and have anti-tumor activities in Phase 2.

Objectives and Endpoints:

Phase	Objectives	Endpoints
Primary		
Phase 1: Dose Escalation	To characterize the safety, tolerability, and dose-limiting toxicities (DLTs), and determine the recommended Phase 2 dose (RP2D) of STAR0602	• Dose-limiting Toxicities (DLTs) • Safety (including but not limited to): treatment emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, clinical laboratory abnormalities per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, and cytokine release syndrome (CRS) per American Society for Transplantation and Cellular Therapy (ASTCT) criteria
Phase 2: Dose Expansion	To further explore anti-tumor activity of STAR0602 as monotherapy and combination with standard chemotherapy in unresectable, locally advanced, or metastatic solid tumors	ORR defined as the proportion of participants who have CR + PR per immune Response Evaluation Criteria in Solid Tumors (iRECIST)
Secondary		
Phase 1: Dose Escalation	To evaluate preliminary anti-tumor activity of STAR0602 in unresectable, locally advanced, or metastatic solid tumors	• ORR according to iRECIST • Duration of response (DOR) defined as time from the date of first documented PR/CR until the first documentation of confirmed disease progression per both iRECIST and Response Criteria in Solid Tumors (RECIST) v1.1 • Disease control rate (DCR) defined as the proportion of participants achieving CR+PR+ stable disease (SD) per both iRECIST and RECIST v1.1
	To evaluate the PK profile of STAR0602 in serum after single- and repeated IV infusions	STAR0602 PK parameters following single- and repeated IV infusions as data permit (e.g., area under the curve [$AUC_{(0-t)}$ and $AUC_{(0-inf)}$] maximum concentration [C_{max}], time to maximum serum concentration [T_{max}], clearance [CL], volume of distribution at steady state [Vss], single-dose half-life [$t_{½}$], and repeat-dose C_{max} and concentration reached immediately before the next dose [C_{trough}])

Phase 2: Dose Expansion	To further evaluate the anti-tumor activity of STAR0602	• ORR per RECIST v1.1 • DOR per both iRECIST and RECIST v1.1 • DCR per both iRECIST and RECIST v1.1 • Progression-free survival (PFS) defined as the time from the initial infusion of study drug until documented disease progression or death from any cause per both iRECIST and RECIST v1.1 • Overall survival (OS)
	To evaluate the PK profile of STAR0602 in serum after single- and repeated IV infusions	STAR0602 population PK parameters in expansion cohorts at the RP2D (e.g., C_{max}, AUC, CL, volume of distribution [Vd])
	To further characterize the safety and tolerability of STAR0602 as monotherapy or in combination with chemotherapy	Safety (including but not limited to): TEAEs, SAEs, deaths, clinical laboratory abnormalities per NCI-CTCAE, Version 5.0, and CRS per ASTCT criteria
Phase 1 and Phase 2: Dose Escalation and Dose Expansion	To assess anti-drug antibody (ADA) formation after IV single- and repeat dose administration of STAR0602	ADA incidence and titers after single- and repeat-IV dosing of STAR0602
Exploratory		
Phase 1: Dose Escalation	To explore the pharmacodynamic effect of STAR0602 treatment on expansion and biology of target Vβ6/Vβ10 T cell subsets in blood and tumor samples at baseline, and during and after treatment with IV STAR0602	• Cell counts and frequency of Vβ6/Vβ10 T cell subsets in peripheral blood mononuclear cells (PBMCs) by flow cytometry • Expression levels of Vβ6/Vβ10 in T cells and other germline Vβ TCR variants in PBMCs and TILs in tumor tissue biopsy samples by gene expression analysis (e.g., using Nanostring assays)
	To assess the levels of serum cytokines and their relationship to pharmacodynamic, safety,	Levels of serum cytokines and other soluble factors (e.g., soluble CD25 [sCD25]) by immunoassay following single- and repeat-dosing of STAR0602

	tolerability, and efficacy endpoints	
	To explore the anti-tumor activity of STAR0602	• PFS per both iRECIST and RECIST v1.1 • OS • ORR, DOR, DCR, PFS per iRECIST and RECIST, and OS in subgroups of TMB-H, MSI-H/dMMR and virally associated cancers, with each subgroup of participants combined across all dose cohorts
Phase 2: Dose Expansion	To explore the pharmacodynamic effect of STAR0602 treatment on expansion and biology of target Vβ6/Vβ10 T cell subsets in blood and tumor samples at baseline, and during and after treatment with IV STAR0602	• Cell counts and frequency of Vβ6/Vβ10 T cell subsets by flow cytometry • Qualitative and semi-quantitative measurement of Vβ6/Vβ10 T cells in tumor tissue by Multiplex IHC/IF • Changes in gene expression profile of T cells isolated from PBMCs, and TILs from tumor tissue • TCR sequencing (TCRseq) of RNA extracted from TILs of the tumor biopsy tissue samples • TIL phenotyping by flow cytometry (will be undertaken at selected sites with experience)
Phase 1 and Phase 2: Dose Escalation and Dose Expansion	To explore the correlation of baseline circulating cell-free tumor DNA (ctDNA) and changes in ctDNA levels with tumor response	ctDNA in the peripheral blood
	To explore dose optimization with Q3W, Q6W dosing schedules or different types of step-up dosing (SUD) on expansion and biology of target Vβ6/Vβ10 T cell subsets in blood and tumor samples at baseline, and during and after treatment with IV STAR0602	• Cell counts and frequency of Vβ6/Vβ10 T cell subsets by flow cytometry • Expression levels of Vβ6/Vβ10 in T cells and other germline Vβ TCR variants in PBMCs and TILs in tumor tissue biopsy samples by gene expression (e.g., using Nanostring assays) • Qualitative and semiquantitative measurement of Vβ6/Vβ10 T cells in tumor tissue by Multiplex IHC/IF • Changes in gene expression profile of T cells isolated from PBMCs, and TILs from tumor tissue • TCR sequencing (TCRseq) of RNA extracted from TILs of the tumor biopsy samples • TIL phenotyping by flow cytometry (will be undertaken at selected sites with experience)
	START-001 is a two-part, open-label, first-in-human (FIH) Phase 1/2 study to determine the safety, tolerability, PK, pharmacodynamics, and preliminary	

Study Design:

anti-tumor activity of STAR0602 as a monotherapy in participants with advanced solid tumors.

The first part (Phase 1) is a dose escalation phase that contains a fixed dose escalation group using a standard 3+3 design (Group A) and a group with a step-up dosing prior to dose escalation using a mBOIN design (Group B) to determine the RP2D (i.e., maximum tolerated dose [MTD] or optimal biological dose [OBD]) for STAR0602 in participants as described below. The second part (Phase 2) is a dose expansion at the RP2D in 9 provisional cohorts of participants whose tumor characteristics are shown in to further assess the safety and anti-tumor activity of STAR0602. For both Phase 1 and Phase 2, participants' tumor status will be evaluated every 8 weeks (56 days) per both iRECIST and RECIST v1.1.

<u>Phase 1 - Dose Escalation:</u>

Phase 1 (Dose Escalation, Group A and Group B) will investigate initial safety, tolerability, PK, pharmacodynamics, and preliminary anti-tumor activity of STAR0602 administered via an IV infusion once every two weeks (Q2W) in participants whose tumors are TMB-H, MSI-H/dMMR, or virally associated. Based on the cumulative assessment of safety and STAR0602 pharmacokinetic and pharmacodynamic data, the dosing schedule may be modified (e.g., once weekly [QW] or once every 3 weeks).

Phase 1 Group A uses a conventional 3 + 3 dose escalation design with a total of eight provisional dose levels of STAR0602 (see the table below). The RP2D will be selected based on integrating safety, clinical activity, PK, and pharmacodynamic data.

Dose Level	STAR0602 Dose (mg/kg)	Number of DLT Evaluable Participants	Comments
A1	0.01	3-6	3 + 3 Design
A2	0.02	3-6	
A3	0.04	3–6	
A4	0.08	3–6	
A5	0.16	3–6	
A6	0.34	3–6	
A7	0.68	3-6	
A8	0.80	3-6	
Total participants for Phase 1 Group A:		Up to 48	

Phase 1 Group A of the study will consist of a Screening Period, a Treatment Period, which includes a DLT Evaluation Period (28-day period after the first STAR0602 administration [Cycle 1]), and a Survival Follow up Period.

Phase 1 Group B incorporates a step-up dosing prior to dose escalation using a modified BOIN (mBOIN) design with a total of 4 provisional dose levels of STAR0602.

Step-up Doses (mg/kg)	**Dose Level**	**STAR0602 Dose (mg/kg)**	**Number of DLT Evaluable Participants**
Step-up 1: 0.01 Step-up 2: A level shown to be safe from Group A (e.g., 0.02 to 0.08)	B1	2-3 times step-up dose 2 (e.g., 0.06 – 0.24)	3–9
	B2	2-3 times B1 (e.g., 0.18 – 0.54)	3–9
	B3	2-3 times B2 (e.g., 0.54 – 0.8)	3–9
	B4	2-3 times B3 but not more than 1.00	3–9
	Total number of participants for Phase 1 Group B:		Up to 36

Phase 1 Group B of the study will consist of a Screening Period, a Treatment Period, which includes a step-up dosing cycle (Cycle 0 D1 and D15 with doses shown to be safe from Group A), and a DLT Evaluation Period (28-day period after the first maintenance dose of STAR0602 [Cycle 1]) for dose escalation, and a Survival Follow-up Period.

Enrollment to Phase 1 Group A and Group B does not need to be sequential, i.e., both groups may enroll concurrently. Information obtained from Group A may inform refinement of step-up doses and dose escalation levels of Group B.

Phase 2 – Dose Expansion:

Once an RP2D is determined from Phase 1, Phase 2 will be initiated to evaluate STAR0602 at this RP2D in up to 10 cohorts totaling 156 to 366 participants who have histologically confirmed solid tumors that are unresectable, locally advanced, or metastatic and for which standard curative therapies do not exist or are no longer effective. These 10 cohorts are provisional and additional cohorts may be added based on the emerging data from the dose escalation phase [Phase 1] and preclinical studies.

The tumor characteristics of these 10 cohorts are described in the table below.

For all cohorts, participants with hepatic metastases will be excluded unless a) adequately treated, either locally (e.g., by surgery, radiofrequency ablation, or chemoembolization) or systemically or both, and stable for 2-3 months, b) ≤ 3

lesions and no lesion ≥ 3 cm in greatest dimension for monotherapy Cohorts 1-7 and 9, or c) Phase 2 Cohort 8 (primary stage 4 or recurrent NSCLC) or Cohort 10 (mCRC with pMMR/MSS without TMB requirement).

In addition, participants with bulky disease defined as any lesion ≥ 5 cm in greatest dimension unless approved by the Sponsor.

Expansion Cohort	Tumor Type and Characteristics	Number of Participants
1	TMB-H (≥ 10 mut/Mb per local site testing)	23-56
2	MSI-H/dMMR cancers (per local site testing)	10-29
3	Colorectal cancer (CRC, both Ras wild- type and mutant) TMB-H, or MSI-H/dMMR, or both TMB-H and MSI-H/dMMR as defined above	23-56
4	Virally associated tumors such as Merkel cell carcinoma, cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancers, or Epstein-Barr Virus (EBV)-related solid tumors	10-29
5	Metastatic triple-negative breast cancer (mTNBC)	10-29
6	Platinum-resistant epithelial ovarian cancer	10-29
7	Metastatic castration-resistant prostate cancer (mCRPC)	10-29
8	Primary stage 4 or recurrent non-small cell lung cancer (NSCLC) (STAR0602 in combination with docetaxel)	25-40
9	Immunogenic tumors (e.g., melanoma, and renal cell carcinoma)	10-29
10	mCRC with pMMR/MSS without TMB requirement (STAR0602 in combination with irinotecan)	25-40

Total Number of Participants	156-366

Each cohort will be evaluated for the primary outcome of safety and ORR, defined as the incidence of confirmed complete or partial responses (CR + PR) per iRECIST. Tumor response assessment will be performed per RECIST v1.1 and per iRECIST.

Phase 2 of the study will consist of a Screening Period, Treatment Period, and Survival Follow-up Period.

Phase 2 Exploratory Dose Optimization

Alternative schedules such as Q3W, Q6W and Step-up Dosing [SUD] may be explored for dose optimization (Section 5.1.3).

Screening Period - Phase 1 and Phase 2:

Screening will occur within 21 days of the first study drug administration. Baseline tumor status will be obtained at Screening using computed tomography (CT) and/or magnetic resonance imaging (MRI) scans plus any necessary tumor markers or other exams. If taken as part of standard of care, CT/MRI within 4 weeks (28 days) prior to first dose may be used.

Treatment Period:

[redacted]

[redacted]

Staggering: Dosing of participants in the Phase 1 Group A and Group B dose escalation part will be staggered such that there is an interval of at least 5 days between initiating treatment of the first and second subject in each new dose escalation (maintenance) cohort.

[redacted]

[redacted]

Dose escalation decisions will be supported by clinical safety and all available PK and pharmacodynamic data during the DLT Evaluation Period. Intermediate dose levels and alternative dosing schedules may be explored during Phase 1, based on review of the cumulative safety data and upon agreement with the Safety Review Committee (SRC). [redacted]

[redacted]

For initial dose optimization, any dose escalation cohort not exceeding the MTD can be expanded to a maximum of 20 participants at that level for further evaluation of safety, PK, pharmacodynamics, dosing schedule, and preliminary anti-tumor activity of STAR0602 to identify an initial optimal dose. The additional group of participants added to a dose escalation cohort are termed backfill participants and their data will not be used for dose escalation decision; however, their data will inform the overall safety profile and optimal dose prior to Phase 2.

In Phase 2, the STAR0602 dose and dosing regimen (RP2D) used for dose expansion will be based on the safety, tolerability, and PK/pharmacodynamic evaluation in Phase 1, dose escalation.

End of Treatment:

[redacted]

End of Study:

[redacted]

Survival Follow-up Period:

	After the EoT visit or 28 days after receipt of the last dose of study drug, all participants (including those discontinued during the DLT evaluation period) who have not withdrawn consent, will enter the Survival Follow-up Period and are to be followed for at least 12 months for survival by electronic methods (e.g., email, EMR review) or telephone communication every 2 months. For the first 2-month follow-up in the Survival Follow-up Period, participants will be required to have an in-clinic visit to obtain required assessments unless the subject has initiated a new anti-cancer treatment.
Rules for Subject Discontinuation:	The investigator may discontinue treating a subject with study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study drug or withdraw from the study at any time for any reason. The reason for discontinuation will be documented. If a subject discontinues study drug, the subject will enter the Follow-Up Period and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the subject withdraws consent. An Investigator may discontinue a subject from the study drug for these primary reasons: • A protocol violation occurs; • AE(s)/ SAE(s); • Pregnancy; • Occurrence of a drug-related DLT; • Drug interruption for ≥ 42 days; • Lost to follow-up; • The Sponsor or Investigator terminates the study; • Withdrawal of consent by subject or proxy; • Other. Participants who are confirmed to have disease progression during the study but otherwise are achieving clinically meaningful benefit may choose to continue the treatment at the discretion of the Investigator, if clinically stable defined as: [redacted] If a subject withdraws consent, the investigator will explain to the subject involved that the study will be discontinued, no additional study drug will be given to the subject, and will provide appropriate medical treatment and other necessary measures for the subject. If a subject is withdrawn from the study or from STAR0602 dosing for any reason other than disease progression, the Sponsor must be alerted within 24 hours.
Dose-Limiting Toxicities:	The severity of AEs will be graded according to the NCI-CTCAE v 5.0 for non-CRS toxicities/infusion reaction while the CRS toxicity will be graded per ASTCT consensus guideline.

	A DLT is defined as any of the following AEs occurring during the DLT Evaluation Period of Cycle 1, which are possibly, probably, or definitely related to the investigational drug and will include:
Eligibility Criteria:	Each subject must meet all of the inclusion criteria and none of the exclusion criteria for this study to be enrolled in the study. **Inclusion Criteria:**

	Participants must have histologically confirmed solid tumors that are unresectable, locally advanced, or metastatic and for which standard curative therapies do not exist or are no longer effective or have intolerable toxicities. Participants should not have received more than three regimens of prior therapies for their advanced or metastatic diseases. For Phase 2 Cohorts 8 and 10 (see below), participants should not have received more than one line of prior therapy. **General:** 1. Age ≥ 18 years old. 2. ECOG performance status of ≤ 1. 3. Ability to provide written informed consent prior to initiation of any study-related tests or procedures that are not part of standard of care for the participant's disease. Participants must also be willing and able to comply with study procedures, including the acquisition of specified research specimens. 4. Life expectancy ≥ 12 weeks. 5. Measurable disease as per RECIST v1.1 criteria and documented by CT and/or MRI. Cutaneous or subcutaneous lesions must be measurable by calipers. Lesions to be used as measurable disease for the purpose of response assessment must either a) not reside in a field that has been subjected to prior radiotherapy, or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment. **Tumor Histology Types:** 6. For Phase 1, participants must have one of the following solid tumors: a. High mutational burden (TMB-H ≥ 10 mut/Mb per local institutional testing); Tumor specimen is preferred, but if not available, liquid biopsy is allowed. If a patient's TMB is between 9-10 mut/Mb, the patient may be eligible for enrollment upon approval by the sponsor; b. MSI-H/dMMR cancer (per local institutional testing); Tumor specimen is preferred, but if not available, liquid biopsy is allowed. c. Virally associated tumors such as Merkel cell carcinoma, cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancers, or Epstein Barr virus (EBV)-related solid tumors. No viral testing required for Merkel cell carcinoma, cervical, or anal cancers. For oropharyngeal, penile, vaginal, and vulvar cancers, human papilloma virus (HPV) positivity documented per local institutional testing is required. For EBV-related solid

	tumors, EBV positivity documented per local institutional testing is required. d. Solid tumors generally considered as immunogenic (e.g., melanoma and renal cell carcinoma) are eligible without prior testing for TMB, MSI or viral status after the Sponsor's approval. 7. For Phase 2, participants must have one of the following solid tumors: 1. High mutational burden (TMB-H ≥ 10 mut/Mb per local site testing); Tumor specimen is preferred, but if not available, liquid biopsy is allowed. If a patient's TMB is between 9-10 mut/Mb, the patient may be eligible for enrollment upon approval by the sponsor; 2. MSI-H/dMMR cancer (per local site testing); Tumor specimen is preferred, but if not available, liquid biopsy is allowed; 3. CRC (both Ras wild-type and mutant) TMB-H, or MSI-H/dMMR, or both TMB-H and MSI-H/dMMR as defined above; 4. Virally associated tumors such as Merkel cell carcinoma, cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancers, or EBV-related solid tumors. No viral testing required for Merkel cell carcinoma, cervical, anal cancers. For oropharyngeal, penile, vaginal, and vulvar cancers, HPV positivity documented per local site testing is required; For EBV-related solid tumors, EBV positivity documented per local institutional testing is required; 5. mTNBC; 6. Platinum-resistant epithelial ovarian cancer; 7. mCRPC; 8. [redacted]

c. [redacted]

9. Solid tumors generally considered as immunogenic (e.g., melanoma and renal cell carcinoma) are eligible without prior testing for TMB, MSI or viral status after the Sponsor's approval.

10. [redacted]

Other tumor histologies may also be included in Phase 2 as additional data emerge to support their inclusion.

Tumor Specimen:

[redacted]

[redacted]

Laboratory Features:

11. Acceptable laboratory parameters as follows:

Albumin ≥ 3.0 g/dL;
Platelet count ≥ 75 × 10^3/µL;
Hemoglobin ≥ 8.5 g/dL;
Absolute neutrophil count ≥ 1.5 × 10^3/µL (participants with duffy-null phenotype who have baseline ANC lower than this criterion may be enrolled upon the approval by the Sponsor);
ALT/AST ≤ 3.0 × ULN; ≤ 5.0 X ULN with hepatic metastases; Phase 2 Cohort 8, ≤ 1.5 ULN)
Total bilirubin ≤ 1.5 × ULN (Phase 2 Cohort 8 < ULN), except participants with Gilbert's syndrome, who may be enrolled if the conjugated bilirubin is within normal limits or approved by the Sponsor;
Calculated creatinine clearance ≥ 50 mL/min based on Cockcroft-Gault formula (Appendix 6) or on a 24-hour urine collection. For over- or under-

	weight participants, ideal body weight should be used for calculating the creatinine clearance. **Reproductive Features:** 12. Female participants of childbearing potential (not surgically sterilized and between menarche and 1-year post-menopause) must have a negative serum (screening) or urine pregnancy test performed within 72 hours prior to the initiation of study drug administration. Female participants of childbearing potential must be willing to use 2 forms of contraception throughout the study, starting with the Screening through 60 days after the last dose of STAR0602. Examples of effective contraception are birth control pills, birth control patch (e.g., Ortho Evra), NuvaRing, intrauterine device, female condom, diaphragm with spermicide, cervical cap, use of a condom by the sexual partner, documented sterile sexual partner or documented evidence of surgical sterilization (e.g., tubal ligation or hysterectomy) at least 6 months prior to Screening. Abstinence is acceptable if this is the established and the preferred contraception method for the subject. It is not necessary to use any other method of contraception when complete abstinence is elected. 13. Male participants with partners of childbearing potential must use barrier contraception from the time of consent through 60 days after last dose of STAR0602 and must not donate sperm during this period. In addition, male participants should also have their partners use contraception (as documented for female participants) for the same period of time. **CNS Metastases:** 14. Symptomatic central nervous system (CNS) metastases must have been treated, be asymptomatic for ≥ 14 days, and meet the following at the time of enrollment: No concurrent treatment for CNS disease (e.g., surgery, radiation, corticosteroids > 10 mg prednisone/day or equivalent); No concurrent leptomeningeal disease or cord compression. **Previous Checkpoint Inhibitor Therapy:** 15. Participants who have previously received a CPI (e.g., anti-programmed death ligand-1 [PD-L1], anti-programmed death-1 [PD-1], anti-cytotoxic T-lymphocyte-associated antigen [CTLA]-4) prior to enrollment must have CPI immune-related toxicity resolved to either Grade ≤ 1 or baseline (prior to the CPI) to be eligible for enrollment. Participants who experienced previous CPI-related endocrine abnormalities are eligible for the study regardless of CTCAE grade if well controlled on replacement therapy. Participants who have had previous CPI-related Grade 3-4 pneumonitis, peri/myocarditis, colitis and bowel perforation, myositis, encephalitis,

	or peripheral neuropathy need to be discussed with and approved by the Sponsor and Medical Monitor. **Exclusion Criteria:** Participants who meet any of the following criteria will be excluded from the study: 1. Participants with a history of known autoimmune disease with exceptions of: Vitiligo; Psoriasis, atopic dermatitis or other autoimmune skin condition not requiring systemic treatment; History of Graves' disease, now euthyroid for > 4 weeks; Hypothyroidism managed by thyroid replacement; Alopecia; Arthritis managed without systemic therapy beyond oral nonsteroidal anti-inflammatory drugs. Adrenal insufficiency well-controlled on replacement therapy. 2. Major surgery or traumatic injury within 8 weeks before first dose of study drug. 3. Unhealed wounds from surgery or injury. 4. Treatment with >10 mg per day of prednisone (or equivalent) or other immune-suppressive drugs within 7 days prior to the initiation of study drug. Exceptions may be made for patients who have had allergic reaction to iodinated contrast media. Steroids for topical, ophthalmic, inhaled, or nasal administration are allowed. 5. Prior therapy within the following timeframe before planned infusion of STAR0602 as follows: [redacted] Note: Concurrent use of hormones either to maintain castrate levels of testosterone in participants with castration-sensitive prostate cancer or for non-cancer-related conditions (e.g., insulin for diabetes, hormone

	replacement therapy) is acceptable. Bisphosphonates are permitted for supportive care of bone metastases (e.g., breast or prostate cancer). 6. Clinically significant cardiovascular/vascular disease including: • Myocardial infarction or unstable angina < 6 months prior to the initiation of study drug; • Clinically significant cardiac arrhythmia (e.g., with potential for hemodynamic instability) not controlled or unresponsive to treatment; • Uncontrolled hypertension: systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg; Participants with systolic blood pressure > 140 mmHg but < 180 mmHg and/or diastolic blood pressure > 90 mmHg but < 100 mmHg may be enrolled upon reviewing co-morbidities/risks and after the sponsor approval. These participants need to be closely monitored with their blood pressure assessed and managed at each visit on treatment; • Pulmonary embolism, stroke, or transient ischemic attack < 6 months prior to initiation of STAR0602; • QTcF (Fridericia correction) prolongation > 480 msec; • Congestive heart failure (New York Heart Association Class III-IV); • Pericarditis/clinically significant pericardial effusion; • Myocarditis; • Vasculitis that has not resolved within 6 months prior to study drug. • Clinically significant gastrointestinal disorders including: • Gastrointestinal perforation < 6 months prior to study drug administration. Participants must have documented evidence (e.g., upper endoscopy, colonoscopy) of completely healed area of prior perforation; • Gastrointestinal bleeding < 2 months prior to study drug administration. Participants must have documented evidence (e.g., upper endoscopy, colonoscopy) of completely healed area of prior bleeding; • Pancreatitis < 6 months prior to the initiation of study drug. Participants must have a CT scan negative for evidence of remaining disease or normal pancreatic enzyme levels for > 4weeks prior to the initiation of study drug; • Diverticulitis flare < 2 months prior to study drug administration. Participants must have a CT scan negative for evidence of remaining disease prior to the initiation of study drug; • History of Crohn's disease or ulcerative colitis. 7. Inflammatory process that has not resolved for ≥ 4 weeks from the date of first study dose. Participants with chronic low-grade inflammatory processes such as radiation-induced pneumonitis are excluded regardless of duration.

	8. Clinically significant pulmonary compromise (e.g., requirement for supplemental oxygen on a continuous basis). 9. Active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to the initiation of study drug. Systemic antiviral, antifungal, or antibacterial therapy must be completed > 1 week prior to the initiation of study drug. Antimicrobial prophylaxis (e.g., for pneumocystis carinii infection) may continue the antimicrobial for that purpose. 10. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study drug administration. Inactivated annual influenza vaccination is allowed. 11. Participants who are known to be human immunodeficiency virus positive or hepatitis B or C positive and have uncontrolled disease. Participants treated for hepatitis C must have viral titers below the limit of quantification to be [redacted] 12. Second primary invasive malignancy not in remission for ≥ 1 year. Exceptions include non-melanoma locally advanced skin cancer, cervical carcinoma in situ, localized prostate cancer (Gleason score ≤ 7), resected melanoma in situ, or any malignancy considered to be indolent and never required systemic therapy, with the exception of indolent lymphomas. 13. Any serious underlying medical or psychiatric condition that would preclude understanding and rendering of informed consent or impair the ability of the subject to receive or tolerate the planned treatment. 14. Known hypersensitivity to STAR0602 or any excipient [redacted] contained in the drug or diluent formulation. 15. Any medical (e.g., requirement of an indwelling catheter such as PleurX or Tenckhoff catheter) or non-medical issue that would contraindicate the participant's participation in the study or confound the results of the study. 16. Pregnant, likely to become pregnant, or lactating women (where pregnancy is defined as the state of a female after conception and until the termination of gestation). 17. [redacted]

	18. [redacted]
Estimated Study Duration:	Participants will be treated with study drug STAR0602 until disease progression or unacceptable toxicity. It is expected that enrollment of the dose escalation (Phase 1) portion of the study will occur over approximately 15 months, and that enrollment of the dose expansion (Phase 2) portion of the study will take approximately 15 months. The total time for conducting this study is expected to be approximately 42 months (including approximately 52 weeks of Survival Follow-up). These estimates of the timing for study conduct may vary from those observed during the actual conduct of the study.
Efficacy Assessments:	Tumor assessments will be obtained at Screening using CT and/or MRI scans plus any necessary tumor markers or other exams at time intervals as specified in the Schedule of Events. Disease status will be evaluated every [redacted] using CT and/or MRI plus tumor markers and other measures as appropriate for the sites of disease, accompanied by physical examination. For both Phase 1 and Phase 2, participants' tumor status will be evaluated every 8 weeks (56 days) per both iRECIST and RECIST v1.1.
Pharmacokinetic, Immunogenicity assessments and Biomarker Studies:	**Pharmacokinetic and Immunogenicity Assessments:** Serum concentrations of STAR0602 will be measured using a bespoke validated immunoassay. The following STAR0602 PK parameters will be evaluated after single- and repeat-dose: **Phase 1** $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, Vss, $t_{½}$, and repeat-dose C_{max} and C_{trough}. **Phase 2:** STAR0602 $AUC_{0\text{-}inf}$, C_{max}, T_{max}, Vss, $t_{½}$, derived from population PK model predictions. Other PK parameters may also be reported, as applicable. [redacted] **Biomarker Studies**: In nonclinical animal studies, the mSTAR1302 surrogate molecule mediates its anti-tumor activity through selectively activating and expanding Vβ6/Vβ10 T cells in blood and in the tumor. Therefore, the Sponsor will measure the following pharmacodynamic biomarkers to assess activity in trial participants: [redacted]

	[redacted] These pharmacodynamic biomarker studies together with PK and safety data and anti-tumor activity will contribute to the improvement of the current trial design and to future studies investigating the safety and efficacy of STAR0602. For Phase 1 dose escalation, a baseline tumor sample and tumor biopsy on study are required only for selected participants but are mandatory for all Phase 2 dose expansion participants.
Safety Assessments and Reporting:	Safety assessments are based on the evaluation of treatment-emergent AEs that occur from the start of the first dose infusion until the EoT Visit or 28 days after the last dose of study drug (whichever is later) or until the subject initiates new anticancer therapy and are determined based on signs, symptoms, physical examination findings and/or laboratory test results from enrolled participants as appropriate. SAEs related to study drug must be reported within 24 hours to the Sponsor, including after the participant's final visit. AEs reported between the time the subject signed the informed consent and the administration of the first dose of study drug will be captured as medical history if not protocol-related. Progression of the underlying neoplasm resulting in hospitalization or death (e.g., subject hospitalized for or dies from PD only, without any other SAE) will be documented as an anti-tumor activity outcome and not as an SAE. If an SAE occurs in a subject and it is unclear whether the event is related to PD, the SAE should be reported. Reporting of laboratory/vital sign abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless any one of the following are met: • Any criterion for an SAE is fulfilled; • A laboratory/vital sign abnormality causes the subject to discontinue from the study drug; • A laboratory/vital sign abnormality causes the subject to interrupt the study drug; • A laboratory/vital sign abnormality requires intervention, including study drug dose interruption or modification. The severity of AEs will be graded according to NCI-CTCAE) v 5.0 for non-CRS toxicities and ASTCT criteria for CRS/infusion reaction toxicities. Safety reports will be reported to Regulatory Agencies per appropriate regulations (e.g., US FDA 21 Code of Federal Regulations 312.32) and to all participating investigators of this study.

Sample Size:	**Phase 1, Dose Escalation** No formal statistical hypotheses are being tested in Phase 1. Analysis of the data obtained from Phase 1 will only utilize descriptive statistical methods. The total number of participants enrolled in Phase 1, Group A and Group B of the dose escalation phase, will depend on the frequency of DLTs and when the RP2D is determined. [redacted] This estimated number of participants does not account for replacement of non-evaluable participants or the possibility of adding backfill participants into any escalation cohort, up to [redacted] to allow for further evaluation of safety, PK, dosing schedule, and anti-tumor activity of STAR0602 at a given dose level below or at the MTD as part of the initial dose optimization plan. **Phase 2, Dose Expansion** [redacted]

	[redacted]
Statistical Methods:	**Statistical Analysis** The statistical analysis will be coordinated by the responsible study biostatistician. A statistical analysis plan will be written to provide details of the endpoint derivations and analysis methods, along with mock tables, listings, and figures. Any changes to the analyses planned in the SAP will be explained in the clinical study report. **General** Summary statistics will consist of the frequencies of each category of discrete variables, and of means, standard deviations, medians, minimum, and maximum values of continuous variables. Safety and anti-tumor activity summaries will be provided by dose level and schedule, and/or by tumor type. Response rates may be calculated for specific disease sub-groups, if appropriate. **Analysis Populations:** Three general populations will be used for the purposes of this analysis for each treatment regimen as defined below: • **Safety Population:** All participants who received at least one dose of the study drug. This population will be used for safety analyses. • **Efficacy Population:** All participants with measurable disease on the baseline tumor assessment who received the planned treatment regimen and had at least 1 post-infusion radiographic tumor assessment. This population will be used for the analysis of efficacy endpoints. • **Response Evaluable Population:** All participants in the Efficacy Population as well as participants who have died within 12 weeks of baseline and had no post-infusion radiographic tumor assessments. The Response Evaluable Population will be used for the primary efficacy ORR analysis.

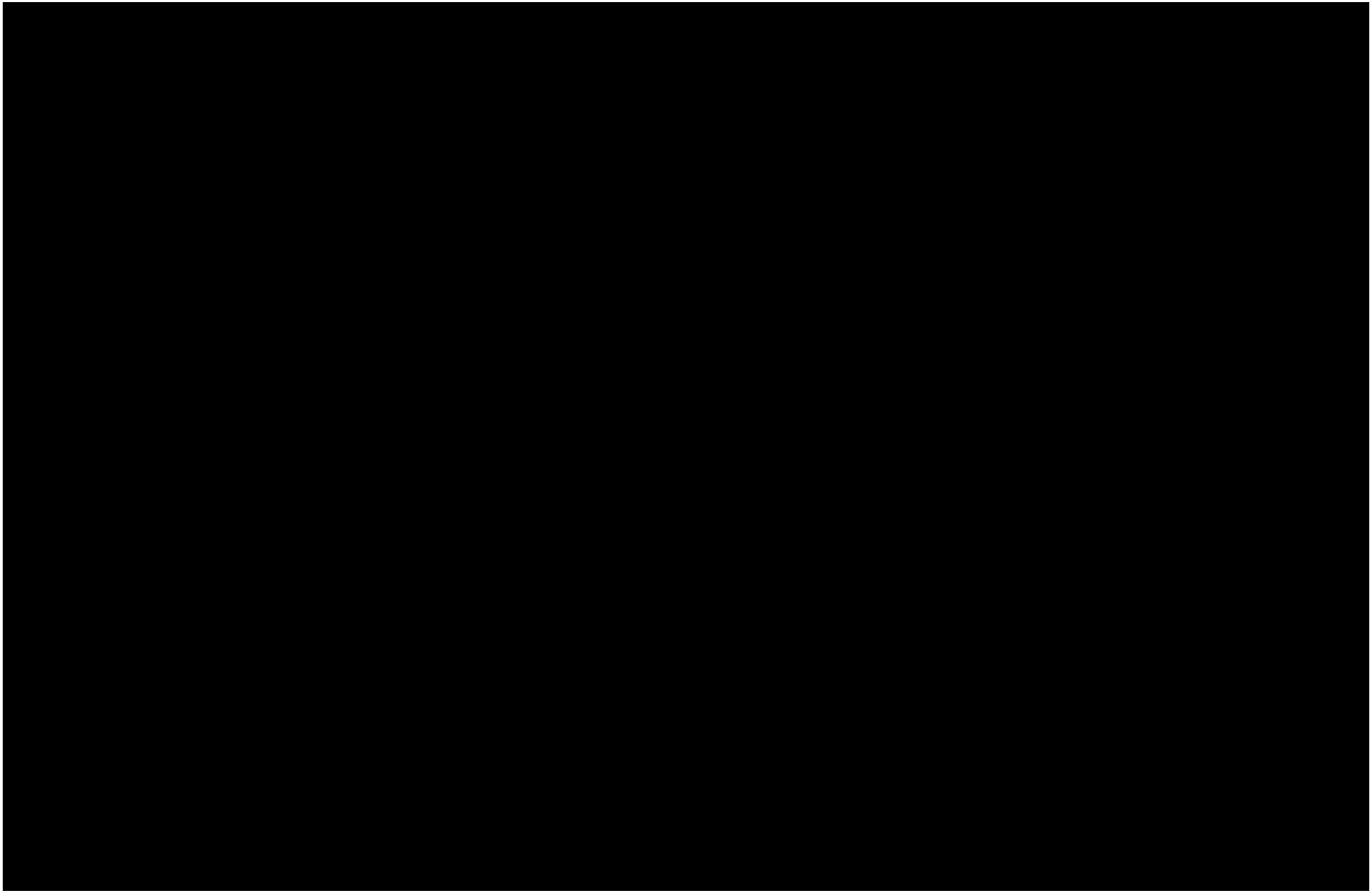
	• **Pharmacokinetic Population:** All participants who received at least one dose of the planned treatment regimen and had at least 1 post-infusion PK assessment. This population will be used for PK analyses. • **Pharmacodynamic Population:** All participants who received at least one dose of the planned treatment regimen and had at least 1 post-infusion pharmacodynamic assessment. This population will be used for pharmacodynamic analyses. • **Immunogenicity Population:** All participants who received at least one dose of the planned treatment regimen and had at least 1 post-infusion- immunogenicity assessment. This population will be used for immunogenicity analyses. **Efficacy** ORR, DOR, DCR, and PFS will be determined per iRECIST. Sensitivity analyses will also be performed using RECIST v1.1 for the following variables. • ORR will be calculated as the proportion of participants who have CR + PR. Exact two-sided 95% CIs will be constructed around the ORRs. • DOR will be defined as time from the date of first documented PR/CR until the first documentation of confirmed disease progression or death whichever occurs first. • DCR will be defined as the proportion of participants who remain free of disease progression (CR + PR + SD). Two sided exact 95% CIs will be constructed around the DCR. • PFS will be calculated as the time from the initial infusion of study drug until documented disease progression or death from any cause. Participants with no PFS event (disease progression or death from any cause) will be censored at the date of their last tumor assessment. Any subject who dies after 2 or more missed assessments will also be censored at the date of their last tumor assessment. Kaplan-Meier estimates will be provided for the median PFS. • OS will be calculated as the time from the initial infusion of study drug to death from any cause. Participants who do not die will be censored at the date that the subject was last known to be alive. Kaplan-Meier estimates will be provided for the median OS. **Safety** General Safety: safety data, including vital signs, ECOG, electrocardiograms (ECGs), laboratory test results, and AEs, will be summarized by dose and assessment time points, as appropriate. Change from baseline will be included in summary tables for laboratory, ECG, and vital sign parameters. Shifts in grade from baseline to maximum post-baseline grade will be summarized for each dose level, as appropriate, for applicable laboratory data. Summaries of participants with AEs Grade ≥ 3 or laboratory values Grade ≥ 3 will be tabulated by dose level, as appropriate.

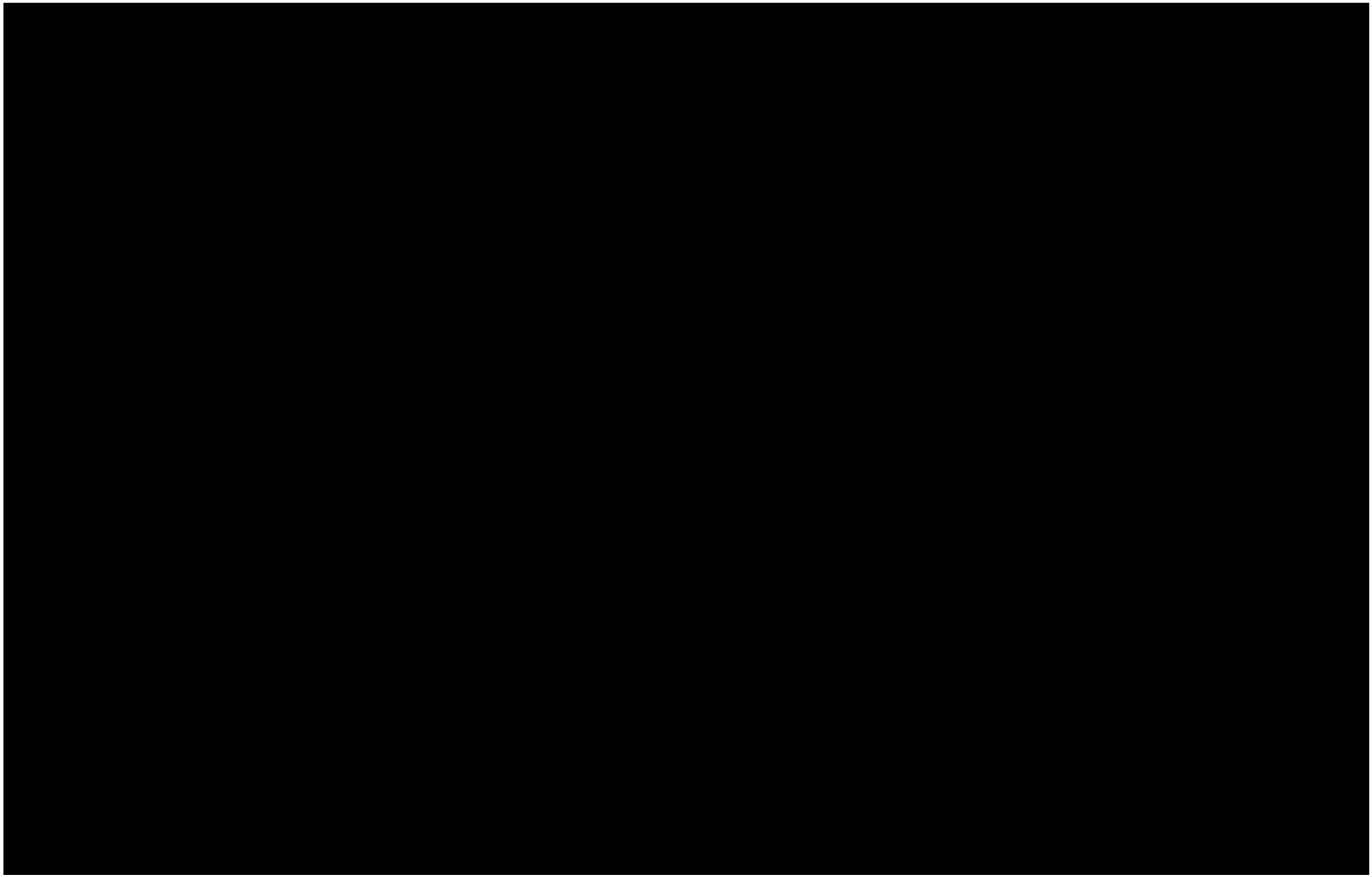
	Statistical Method for Phase 1 Dose Escalation and MTD determination: [redacted] **Other Assessments or Analyses** PK, pharmacodynamic markers, immunogenicity summaries will be provided by initial dose cohort in Part 1 and by expansion cohort in Part 2. PK parameters will be evaluated and summarized for each dose cohort in Part 1 and in Part 2 and presented graphically. Pharmacodynamic markers: Changes from baseline in pharmacodynamic markers will also be evaluated and summarized for each dose cohort in Part 1 and for Part 2 and presented graphically.
Safety Review Committee:	The SRC will consist of: 1. Site physicians 2. Company physicians 3. Contract research organization physician 4. Statistician 5. Independent (from Sponsor) pharmacovigilance safety expert(s) 6. Any other independent expert (e.g., PK or toxicologist) on an as-needed basis All dose escalation decisions will be made by the SRC. Additionally, the SRC will continue safety monitoring in the expansion cohorts with consistent safety data reviews and specified time points during enrollment.
Date of Protocol:	08 May 2026

2. SCHEDULES OF EVENTS

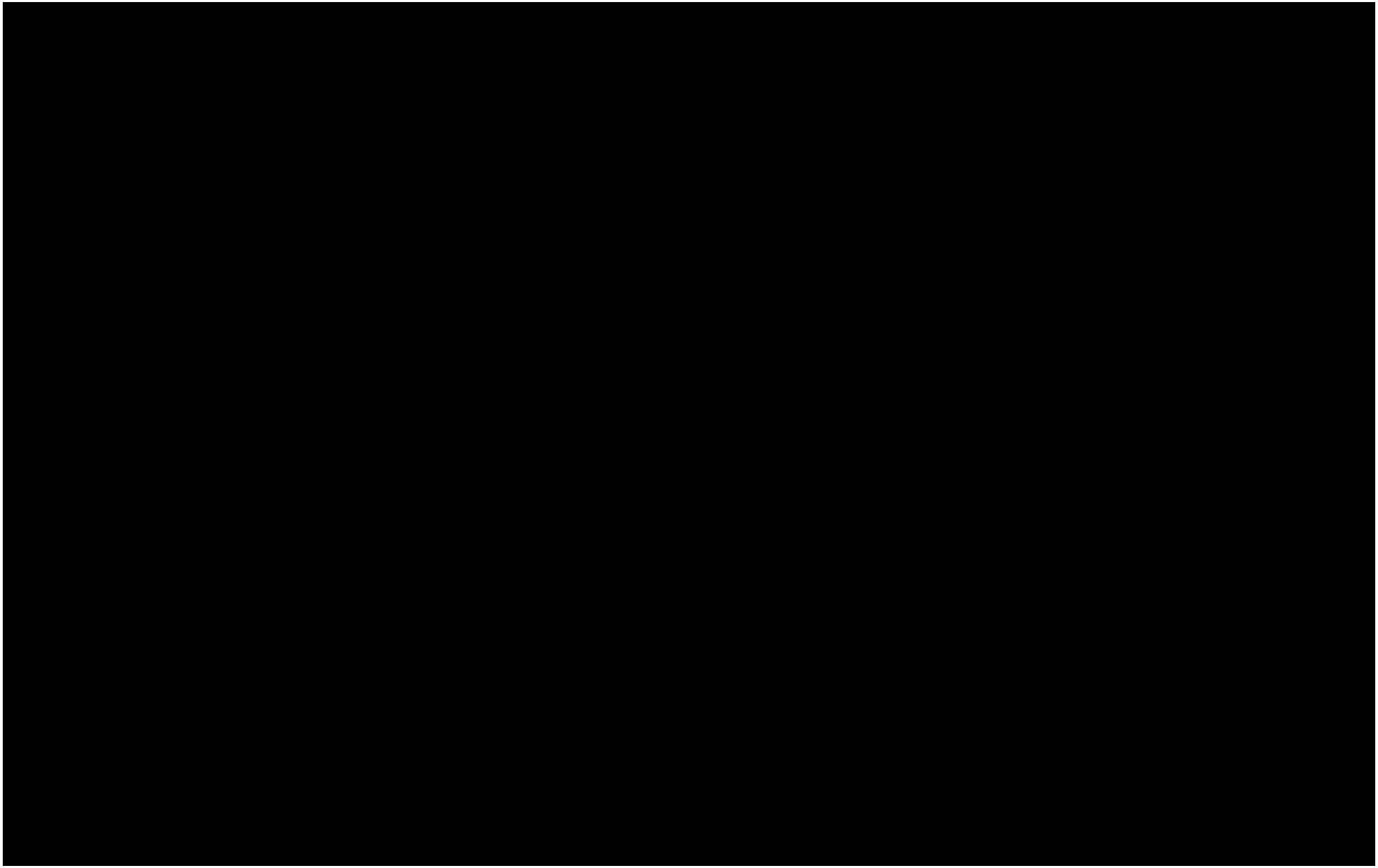
Table 1 Schedule of Events: Phase 1 Group A (Fixed, Q2W Dosing and 3+3 Design, 28-Day Cycle)

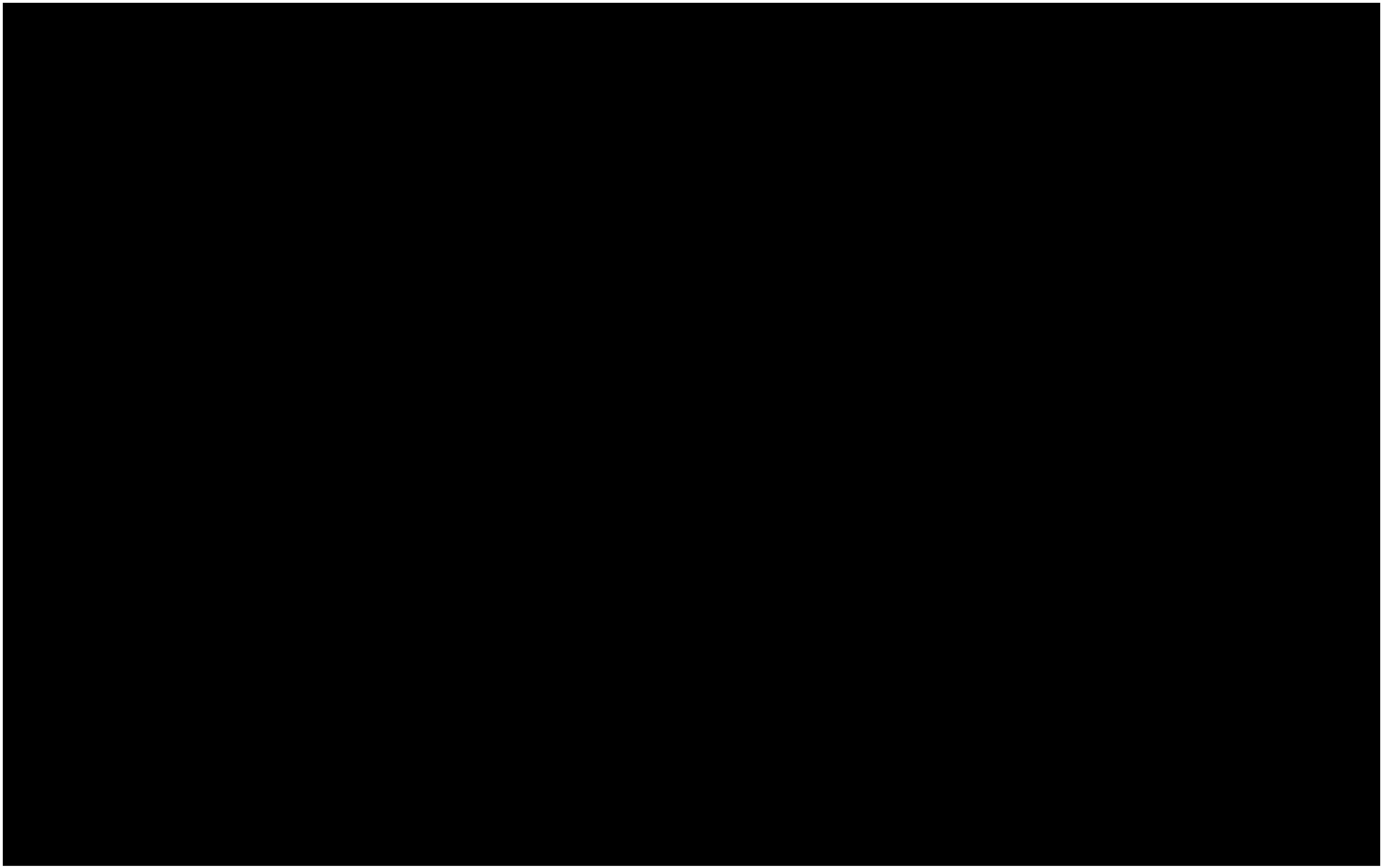


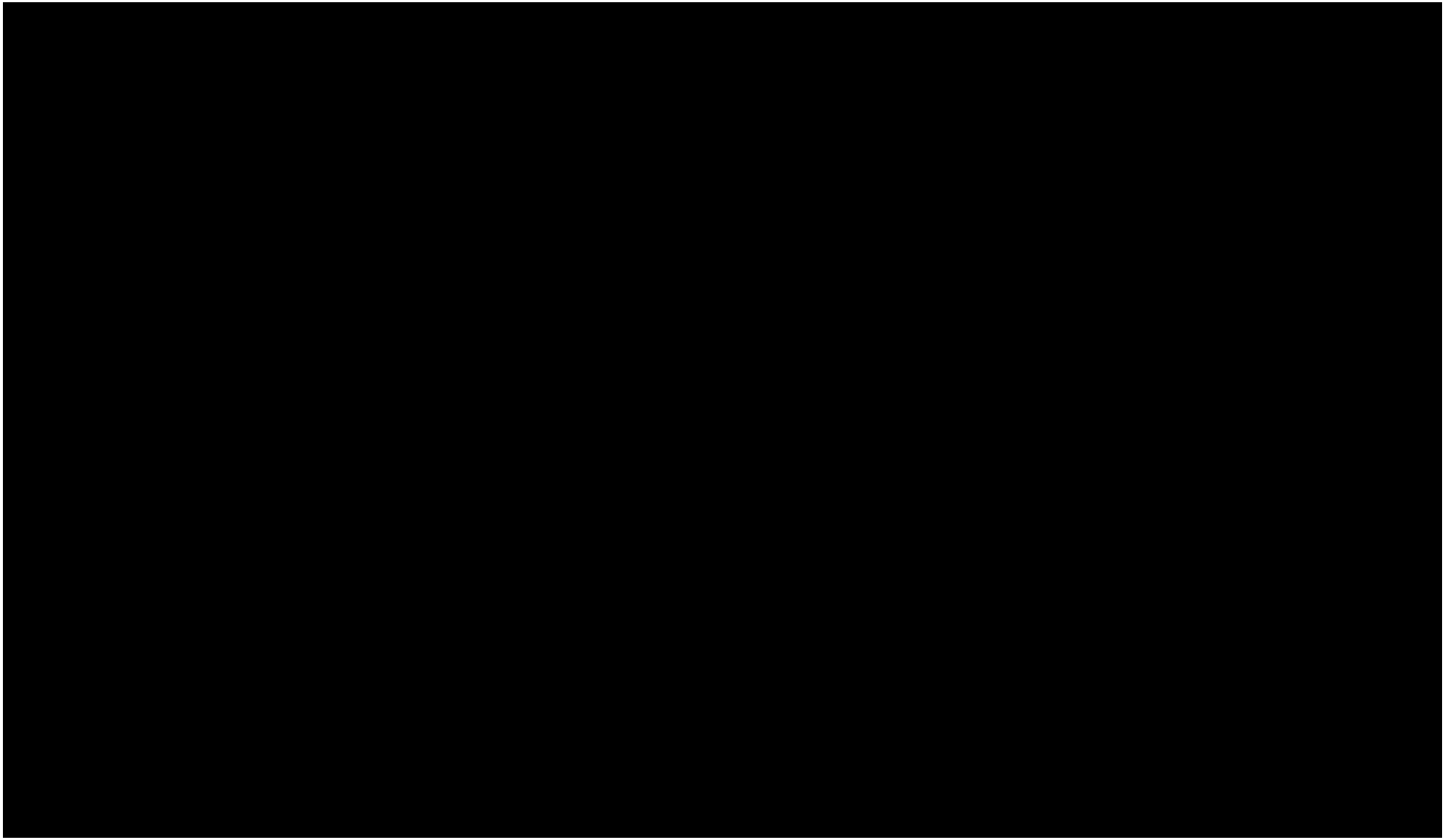






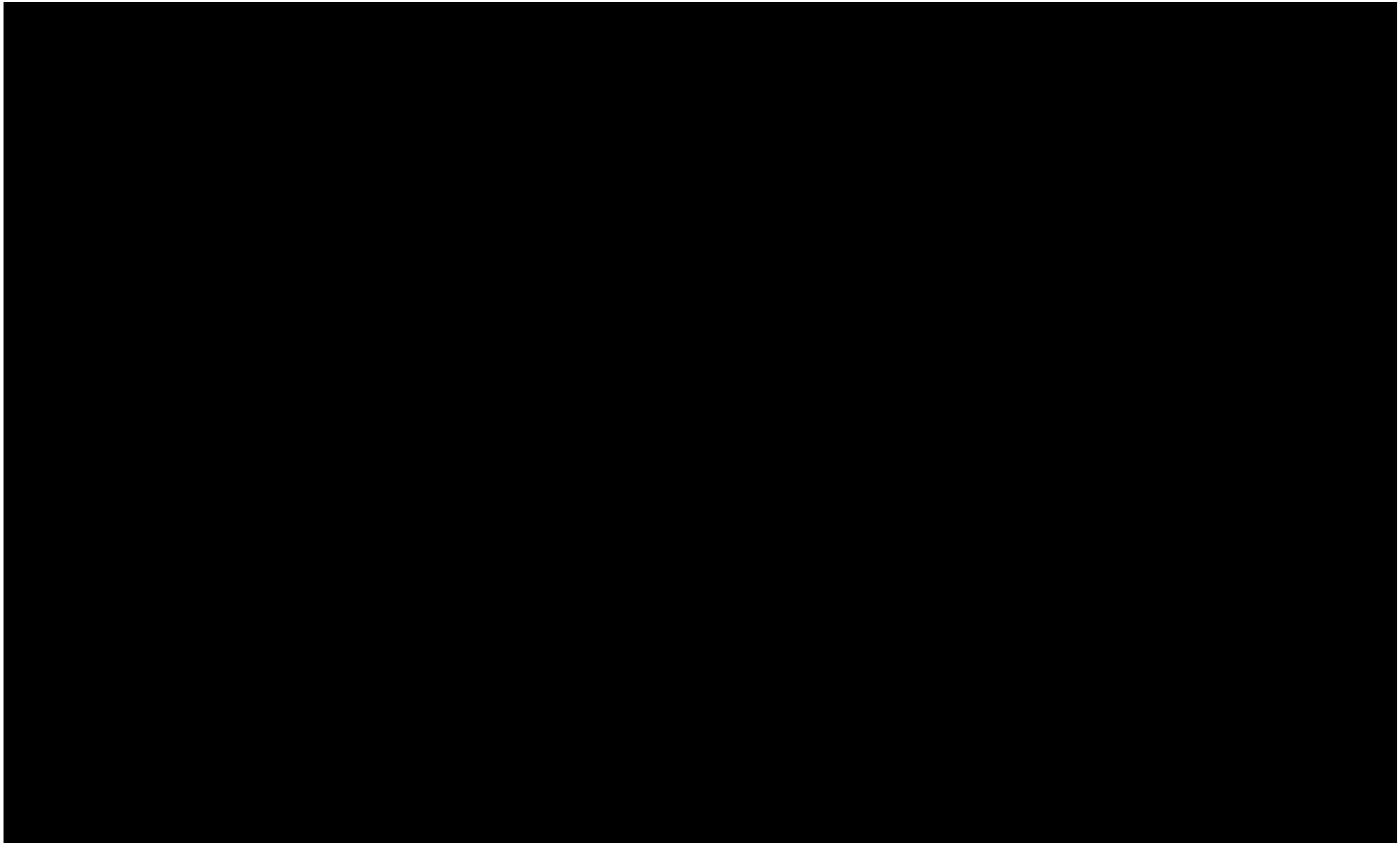




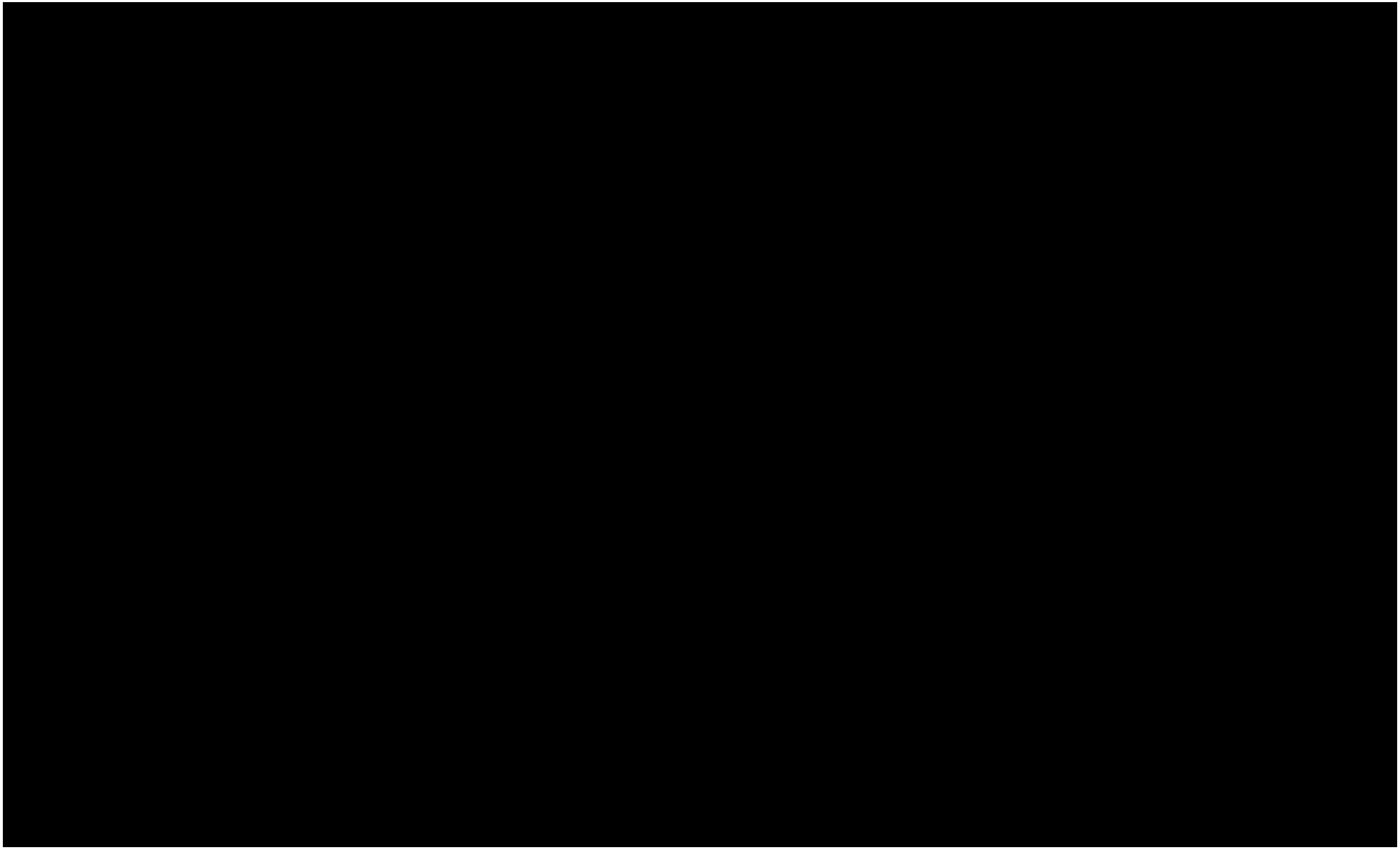


[redacted]

[redacted]



[redacted]





3. INTRODUCTION

3.1. Background

Cancer immunotherapy has revolutionized the field of oncology over the past decade by prolonging survival of some patients with fatal cancers. Recent successes of immunotherapy, evidenced by multiple approvals in many cancer indications[1], are built on the ability of immunotherapeutic agents to enhance the anti-tumor activity of endogenous T cells by either blocking inhibitory T cell checkpoint receptors (e.g., checkpoint inhibitors [CPIs]) or by activating the T cell receptors (e.g., bi-specific T cell engagers [TCEs] Nathan et al., 2021). Studies also suggest that increased tumor antigen levels are associated with better response to immunotherapies (Rousseau et al., 2021), which rationalizes why CPIs are most efficacious in antigen-rich, immunologically "hot" tumors (Yarchoan et al., 2017). However, despite the abundant presence of tumor antigens (i.e., high tumor mutational burden [TMB-H], microsatellite instability [MSI], and viral antigens), and likely correlates to enhanced antigen-specific T cell responses (e.g., programmed death-ligand 1 [PD-L1] expression [Xu et al., 2019]), CPI treatment only benefits approximately a third of patients and elicits durable responses in only a minority of patients, with most relapsing after 6 to 12 months (Barrueto et al., 2020). Thus, CPI treatment failure emerges as a significant high unmet medical need. Therefore, novel treatment strategies that focus on further boosting endogenous T cells through alternative mechanisms are needed to overcome resistance to current CPI therapies, improve responses in patients with immunologically "cold" tumors, and reduce toxicities associated with TCEs. One of such alternative novel strategies is the selective T cell activation repertoire (STAR) bi-specific platform exemplified by STAR0602 the Sponsor is currently developing.

STAR0602 is a bifunctional antibody-fusion molecule comprising an antibody Fab region (antibody arm) that binds to a subset of human αβ T cells expressing the germline-encoded variable (V) β6 and variable (V) β10 chains of the T cell receptor (TCR) and a physiologically active, unmodified human interleukin-2 (IL-2) molecule (the other binding arm), fused to the IgG1 Fc domain of the antibody. The Fc domain of STAR0602 contains an N297A mutation to prevent interaction with Fc receptors.

STAR0602 targets the Vβ6/Vβ10 T cell subset. Vβ6 and to lesser extent Vβ10 have previously been reported as some of the most commonly found germline Vβ TCR variants identified from transcriptomic analysis of The Cancer Genome Atlas (TCGA) database with combined relative abundance of ~8-10% reported (Li et al., 2016). Additional reports have consistently reported TRBV6-5 as one of the most frequently used germline Vβ TCRs in the peripheral blood (Omer et al., 2022; Kitaura et al., 2016). This observation was confirmed by Marengo's flow cytometry analysis of peripheral blood mononuclear cells (PBMCs) using Marengo's internal antibody recognizing common Vβ6/Vβ10 T cells, which showed a frequency of ~ 6% Vβ6/Vβ10 T cells in PBMCs obtained from healthy donors.

3.2. STAR0602 Mechanism of Action

[redacted]

[1] https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications

[redacted]

3.3. Preclinical Studies

[redacted]

[redacted]

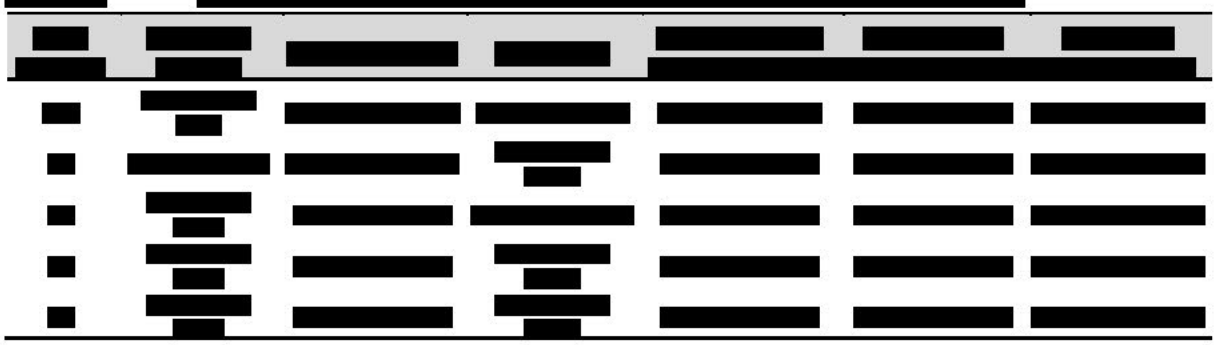


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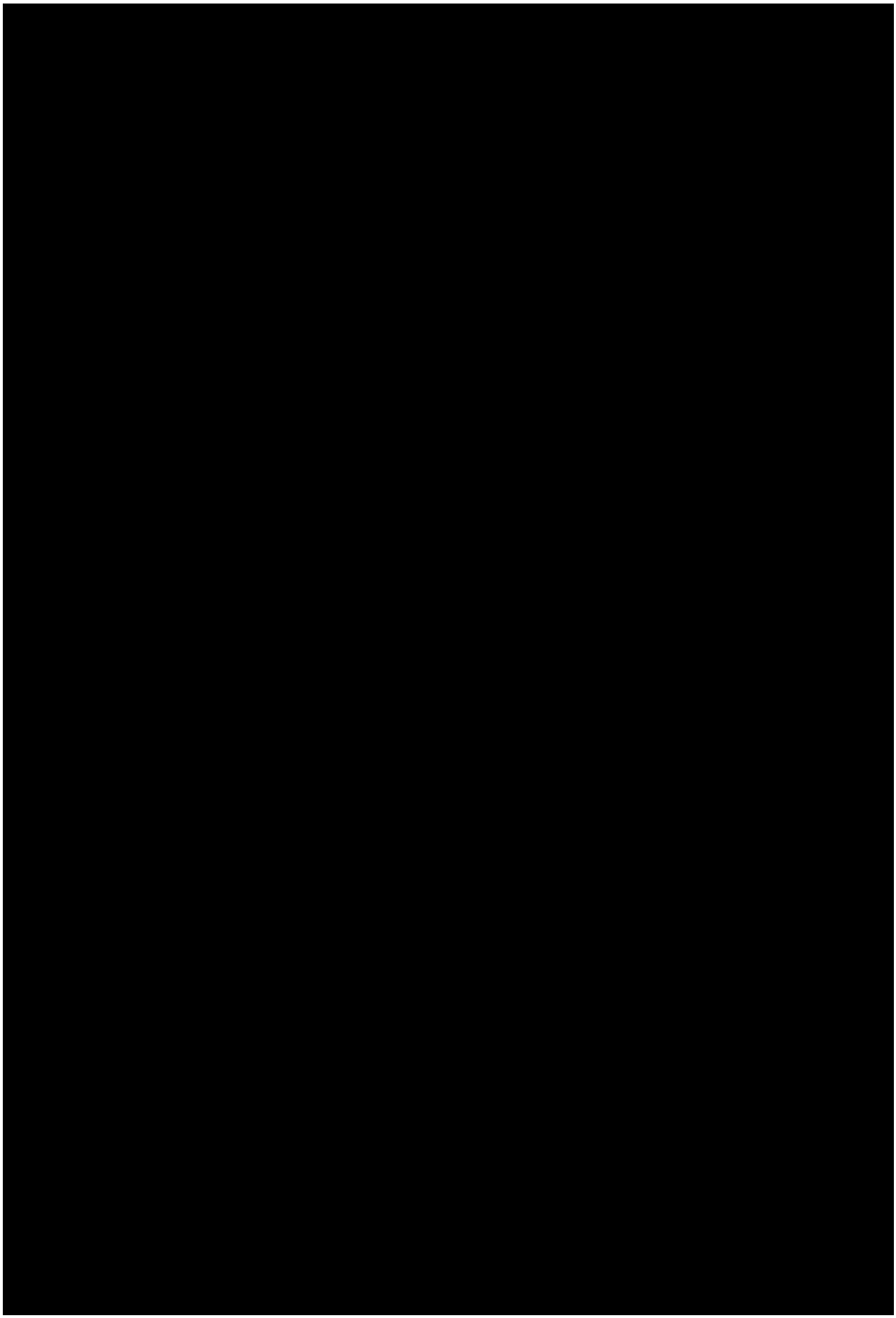


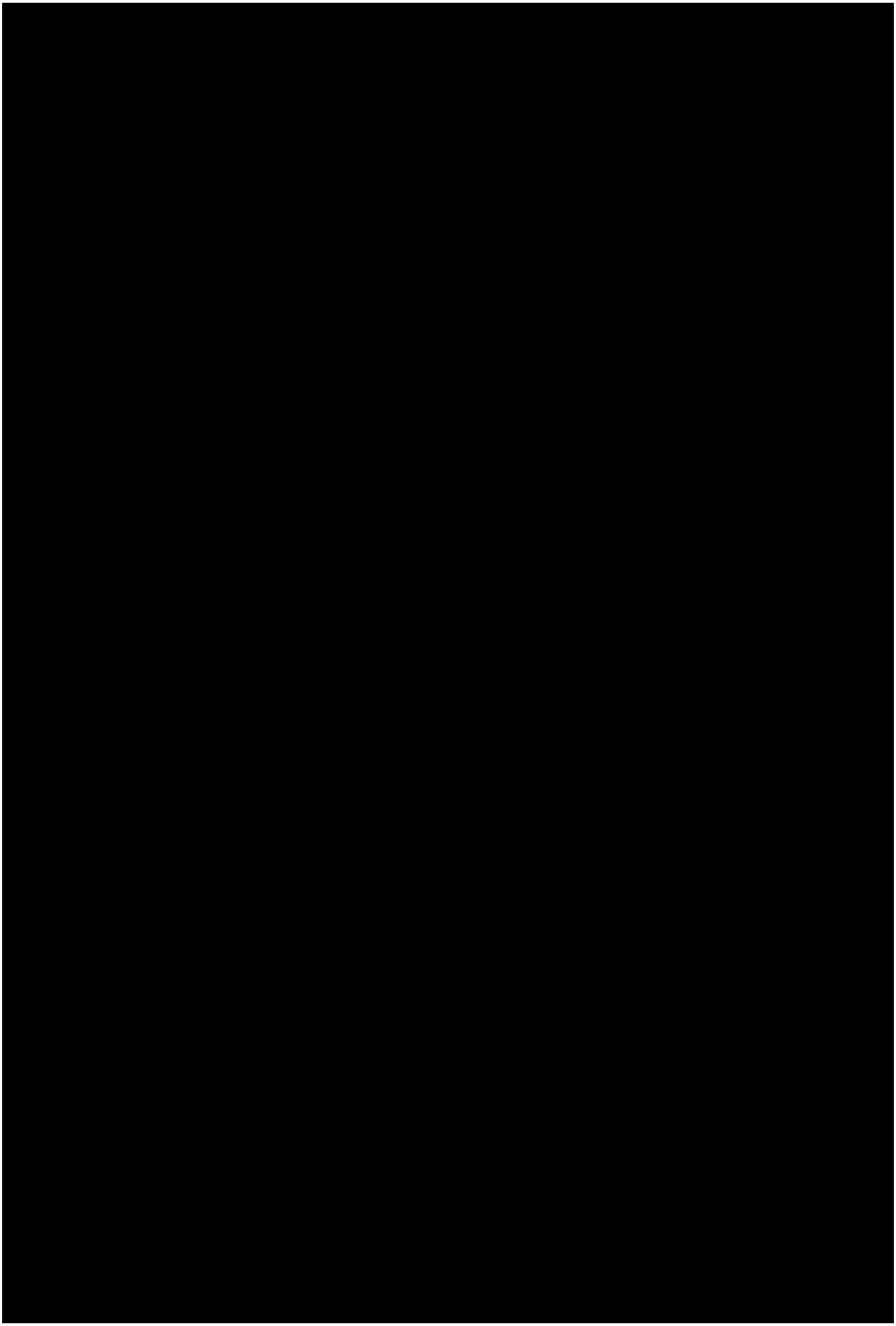
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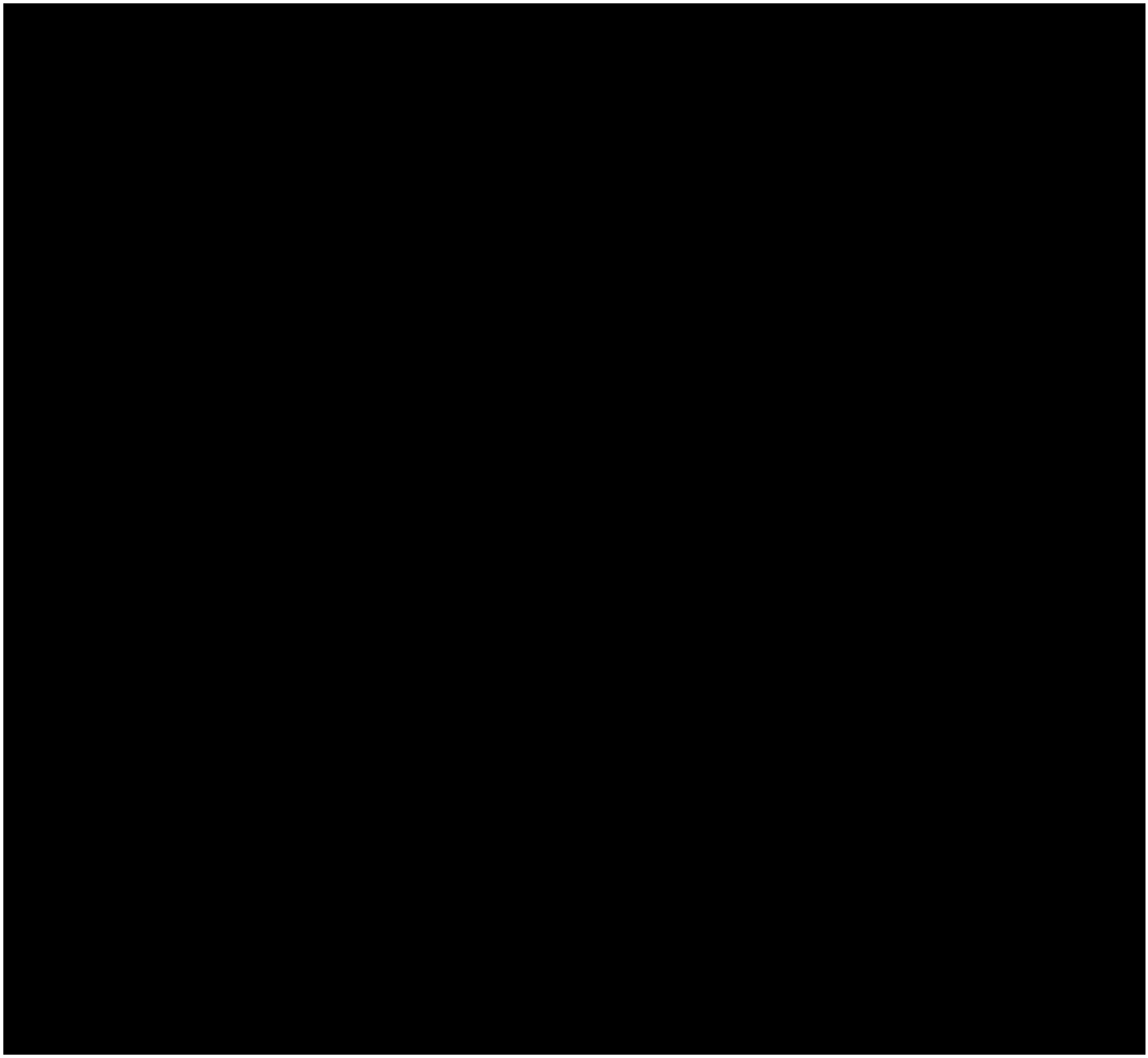
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Preclinical studies described above indicate that STAR0602 represents a novel therapeutic strategy and provide a strong scientific rationale to investigate its potential effectiveness and safety in humans. Thus, the Sponsor is proposing trial START-001, titled "A Phase 1/2, First-in-Human, Open-Label, Dose Escalation and Expansion Study of STAR0602, a Selective T Cell Receptor (TCR)-targeting, Bifunctional Antibody-fusion Molecule, in Participants with Unresectable, Locally Advanced, or Metastatic Solid Tumors that are Antigen-rich (START-001)."

In addition, STAR0602 in combination with standard chemotherapy may be beneficial. Chemotherapy can cause immunogenic death and potentiate the STAR0602 effect on T cell activation and proliferation which may potentially turn the immune "cold" tumors into a "hot" immune environment as suggested by pre-clinical studies[2,3]. Therefore, such a combination could have additive/synergistic potential leading to improved responses and prolongation to PFS and OS, providing a strong rationale to investigate STAR0602 in combination with

[2] https://pubmed.ncbi.nlm.nih.gov/41151838/
[3] https://www.esmoopen.com/article/S2059-7029(25)00036-5/fulltext

docetaxel in primary stage 4 or recurrent non-small cell lung cancer (NSCLC, Phase 2 Cohort 8) and irinotecan in mCRC with pMMR/MSS without TMB requirement (Phase 2 Cohort 10).

3.5. Benefit/Risk Assessment

This FIH study plans to enroll a study population of participants who have unresectable, locally advanced, or metastatic solid tumors for which standard curative therapies do not exist or are no longer effective, including therapies with CPIs which often represent the limited, if not the last, options. Therefore, these participants have a high unmet medical need and STAR0602, a novel immunotherapeutic agent, may offer a promising new option for these participants (Johnson et al., 2023)

As described in previous sections and recent publications (Hsu et al., 2023; Vantourou et al., 2023), the Sponsor has shown that STAR0602: 1) has a novel mechanism of action in selectively activating and expanding memory T cells, generally thought to be critical for mediating and maintaining tumor regression in vivo; 2) has demonstrated ex vivo anti-tumor activities and its murine surrogate has led to eradication of established tumors and long-term maintenance of tumor-free status (cure); 3) activates T cells with a different cytokine expression profile than anti-CD3 T cell engagers (TCEs) based on published reports and thus may cause lower toxicities; and 4) has been shown to be generally well tolerated in cynomolgus monkeys. In addition, the proposed starting dose for this trial based on the minimally anticipated biological effect level (MABEL) approach (see Section 5.2) is [redacted]-fold lower than the NOAEL and [redacted]-fold lower than the 1/6 of HNSTD determined from these NHP studies. NHP studies also indicated that IV STAR0602 had its intended pharmacological effects of activating T cells and expanding Vβ6/Vβ10 CD8+ T cell in vivo.

Taken together, the Sponsor concludes that the potential benefit provided by STAR0602, a novel T cell activator with potent anti-tumor activity demonstrated in the preclinical studies and with good tolerability in NHP studies, outweighs the potential risks in the planned study population in this FIH study.

4. STUDY OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are provided in Table 6.

Table 6 Study Objectives and Endpoints

Phase	Objectives	Endpoints
Primary		
Phase 1: Dose Escalation	To characterize the safety, tolerability, and dose-limiting toxicities (DLTs), and determine the recommended Phase 2 dose (RP2D) of STAR0602	• DLTs • Safety (including but not limited to): treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, clinical laboratory abnormalities per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, and CRS per American Society for Transplantation and Cellular Therapy (ASTCT) criteria
Phase 2: Dose Expansion	To further explore anti-tumor activity of STAR0602 as monotherapy and combination with standard chemotherapy in unresectable, locally advanced, or metastatic solid tumors	Overall response rate (ORR) defined as the proportion of participants who have complete response (CR) + partial response (PR) per immune response evaluation criteria in solid tumors (iRECIST)
Secondary		
Phase 1: Dose Escalation	To evaluate preliminary anti-tumor activity of STAR0602 in unresectable, locally advanced, or metastatic solid tumors	• ORR according to iRECIST • Duration of response (DOR) defined as time from the date of first documented PR/CR until the first documentation of confirmed disease progression per both iRECIST and RECIST v1.1 • Disease control rate (DCR) defined as the proportion of participants achieving CR+PR+ SD per both iRECIST and RECIST v1.1
	To evaluate the PK profile of STAR0602 in serum after single- and repeated IV infusions	STAR0602 PK parameters following single- and repeated IV infusions as data permit (e.g., area under the curve [$AUC_{(0-t)}$ and $AUC_{(0-inf)}$] maximum concentration [C_{max}], time to maximum serum concentration [T_{max}], clearance [CL], volume of distribution at steady state [Vss], single-dose half-life [$t_{½}$], and repeat-dose C_{max} and concentration reached immediately before the next dose [C_{trough}])

Phase 2: Dose Expansion	To further evaluate the anti-tumor activity of STAR0602	• ORR per RECIST v1.1 • DOR per both iRECIST and RECIST v1.1 • DCR per both iRECIST and RECIST v1.1 • Progression-free survival (PFS) defined as the time from the initial infusion of study drug until documented disease progression or death from any cause per both iRECIST and RECIST v1.1 • Overall survival (OS)
	To evaluate the PK profile of STAR0602 in serum after single- and repeated IV infusions	STAR0602 population PK parameters in expansion cohorts at the RP2D (e.g., C_{max}, AUC, CL, volume of distribution [Vd])
	To further characterize the safety and tolerability of STAR0602 as monotherapy or in combination with chemotherapy	Safety (including but not limited to): TEAEs, SAEs, deaths, clinical laboratory abnormalities per NCI-CTCAE, Version 5.0, and CRS per ASTCT criteria
Phase 1 and Phase 2: Dose Escalation and Dose Expansion	To assess ADA formation after IV single- and repeat dose administration of STAR0602	ADA incidence and titers after single- and repeat-IV dosing of STAR0602
Exploratory		
Phase 1: Dose Escalation	To explore the pharmacodynamic effect of STAR0602 treatment on expansion and biology of target Vβ6/Vβ10 T cell subsets in blood and tumor samples at baseline, and during and after treatment with IV STAR0602	• Cell counts and frequency of Vβ6/Vβ10 T cell subsets in PBMCs by flow cytometry • Expression levels of Vβ6/Vβ10 in T cells and other germline Vβ TCR variants in PBMCs and TILs in tumor tissue biopsy samples by gene expression (e.g., using Nanostring assays)
	To assess the levels of serum cytokines and their relationship to pharmacodynamic, safety, tolerability, and efficacy endpoints	Levels of serum cytokines and other soluble factors (e.g., sCD25) by immunoassay following single- and repeat-dosing of STAR0602
	To explore the anti-tumor activity of STAR0602	• PFS per both iRECIST and RECIST v1.1 • OS • ORR, DOR, DCR, PFS per iRECIST and RECIST, and OS in subgroups of TMB-H, MSI-H/dMMR and virally associated cancers, with each subgroup of participants combined across all dose cohorts

Phase 2: Dose Expansion	To explore the pharmacodynamic effect of STAR0602 treatment on expansion and biology of target Vβ6/Vβ10 T cell subsets in blood and tumor samples at baseline, and during and after treatment with IV STAR0602	• Cell counts and frequency of Vβ6/Vβ10 T cell subsets by flow cytometry • Expression levels of Vβ6/Vβ10 in T cells and other germline Vβ TCR variants in PBMCs and TILs in tumor tissue biopsy samples by gene expression (e.g., using Nanostring assays) • Qualitative and semiquantitative measurement of Vβ6/Vβ10 T cells in tumor tissue by Multiplex IHC/IF • Changes in gene expression profile of T cells isolated from PBMCs, and TILs from tumor tissue • TCR sequencing (TCRseq) of RNA extracted from TILs of the tumor biopsy samples • TIL phenotyping by flow cytometry (will be undertaken at selected sites with experience)
	To further explore the anti-tumor activity of STAR0602	• ORR defined as the proportion of participants who have CR + PR per iRECIST from subgroup analyses (e.g., pooled analyses for TMB-H or MSI-H or both regardless of tumor histologies) at the Sponsor's discretion
Phase 1 and Phase 2: Dose Escalation and Dose Expansion	To explore the correlation of circulating cell -free tumor DNA (ctDNA) with tumor response	ctDNA in the peripheral blood
	To explore dose optimization with Q3W, Q6W dosing schedules or different types of step-up dosing (SUD) on expansion and biology of target Vβ6/Vβ10 T cell subsets in blood and tumor samples at baseline, and during and after treatment with IV STAR0602	• Cell counts and frequency of Vβ6/Vβ10 T cell subsets by flow cytometry • Expression levels of Vβ6/Vβ10 in T cells and other germline Vβ TCR variants in PBMCs and TILs in tumor tissue biopsy samples by gene expression (e.g., using Nanostring assays) • Qualitative and semiquantitative measurement of Vβ6/Vβ10 T cells in tumor tissue by Multiplex IHC/IF • Changes in gene expression profile of T cells isolated from PBMCs, and TILs from tumor tissue

		• TCR sequencing (TCRseq) of RNA extracted from TILs of the tumor biopsy samples • TIL phenotyping by flow cytometry (will be undertaken at selected sites with experience)

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan

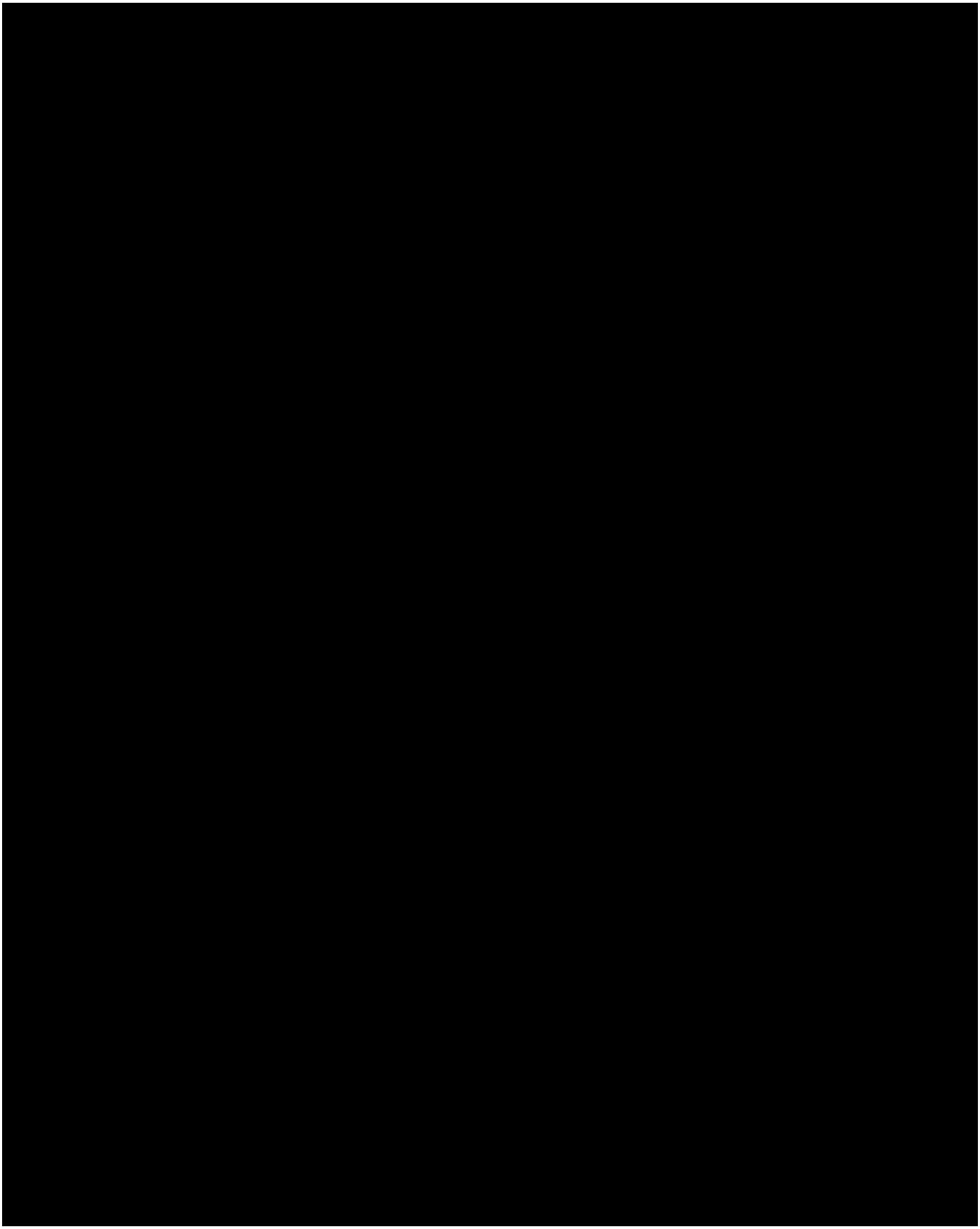
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5.1.1. Phase 1: Dose Escalation

[redacted]

5.1.1.1. Phase 1 Group A

[redacted]

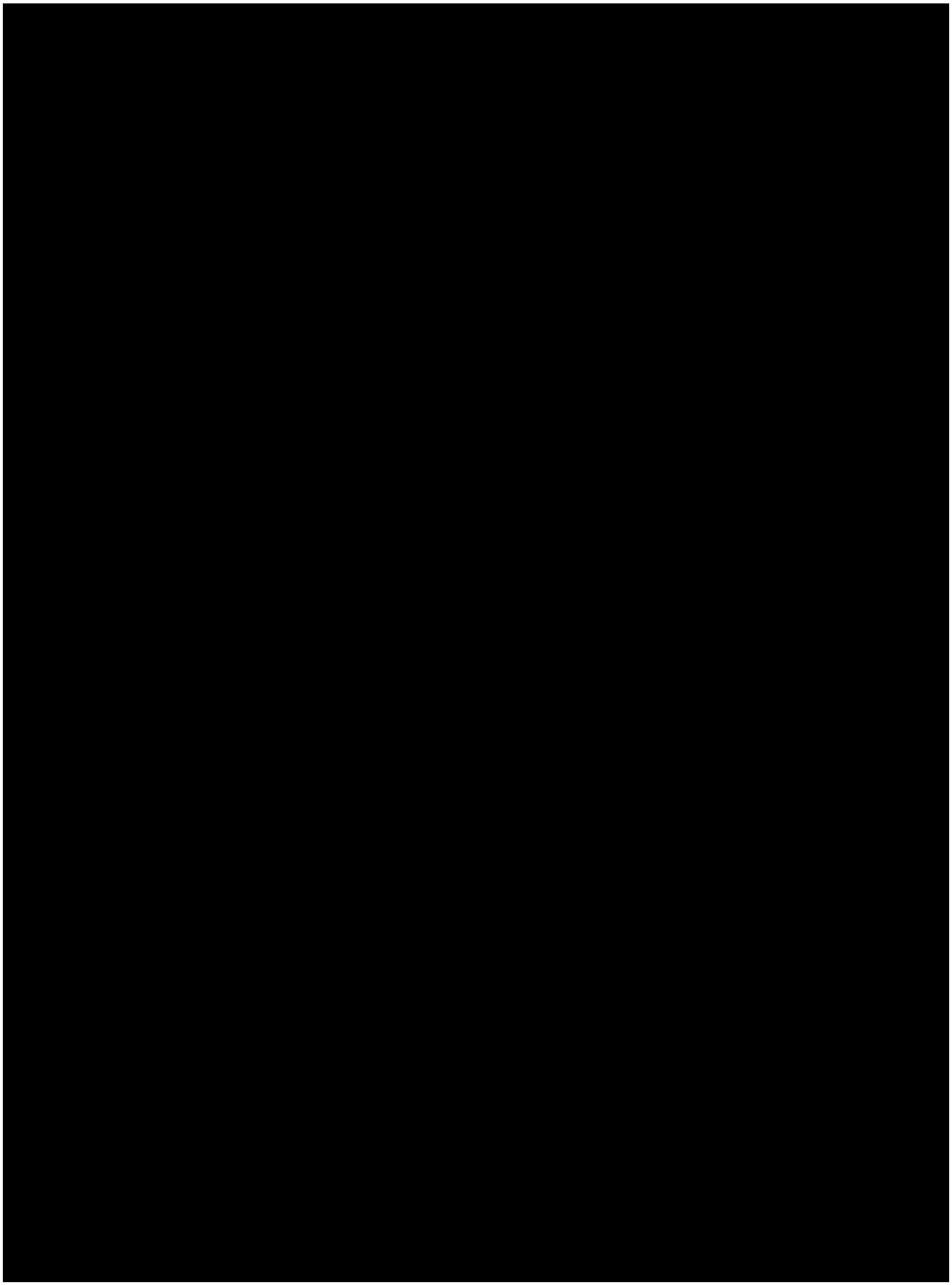


[redacted]

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[redacted]

5.1.8. End of Study

[redacted]

[redacted]

[redacted]

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[redacted]

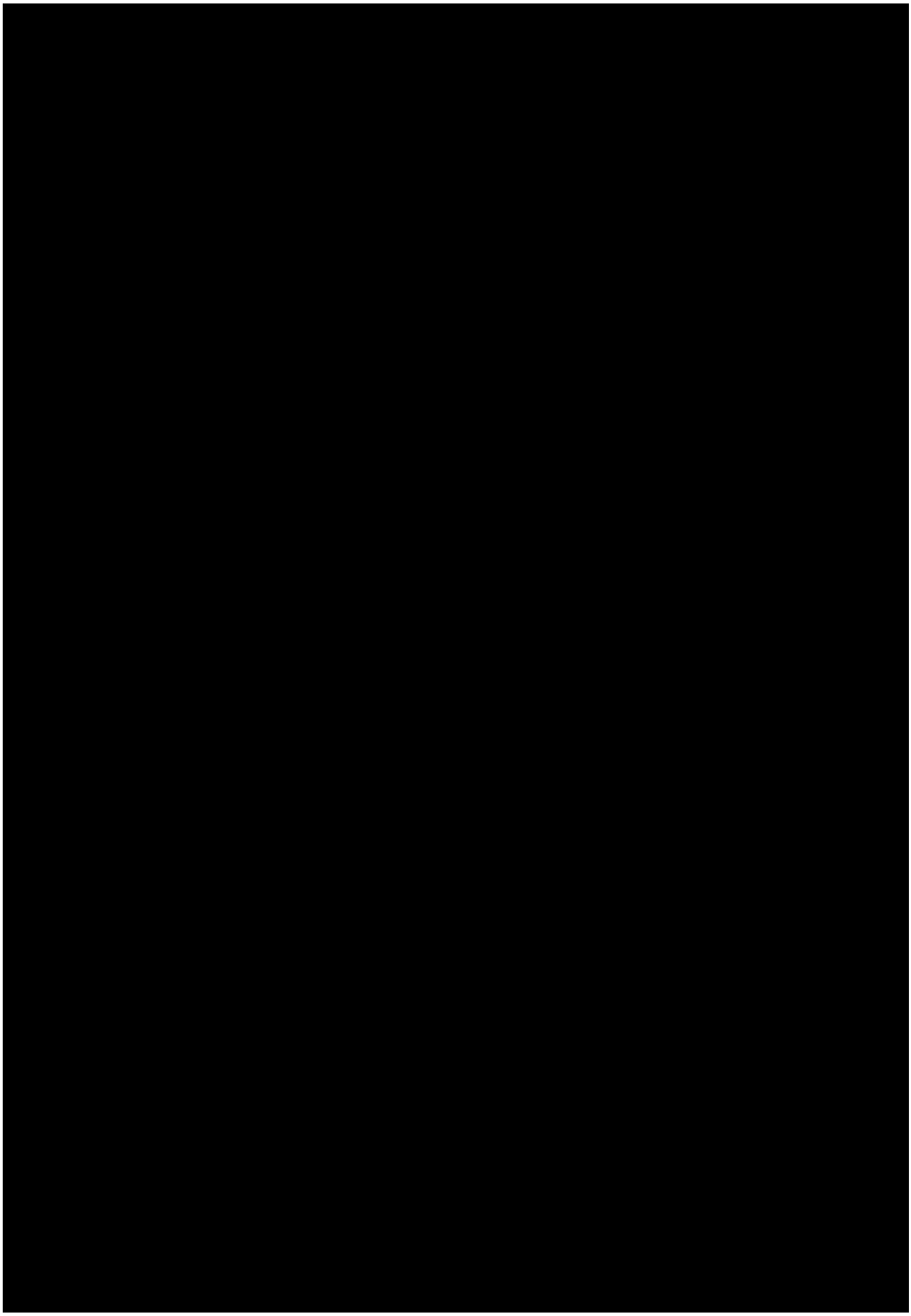
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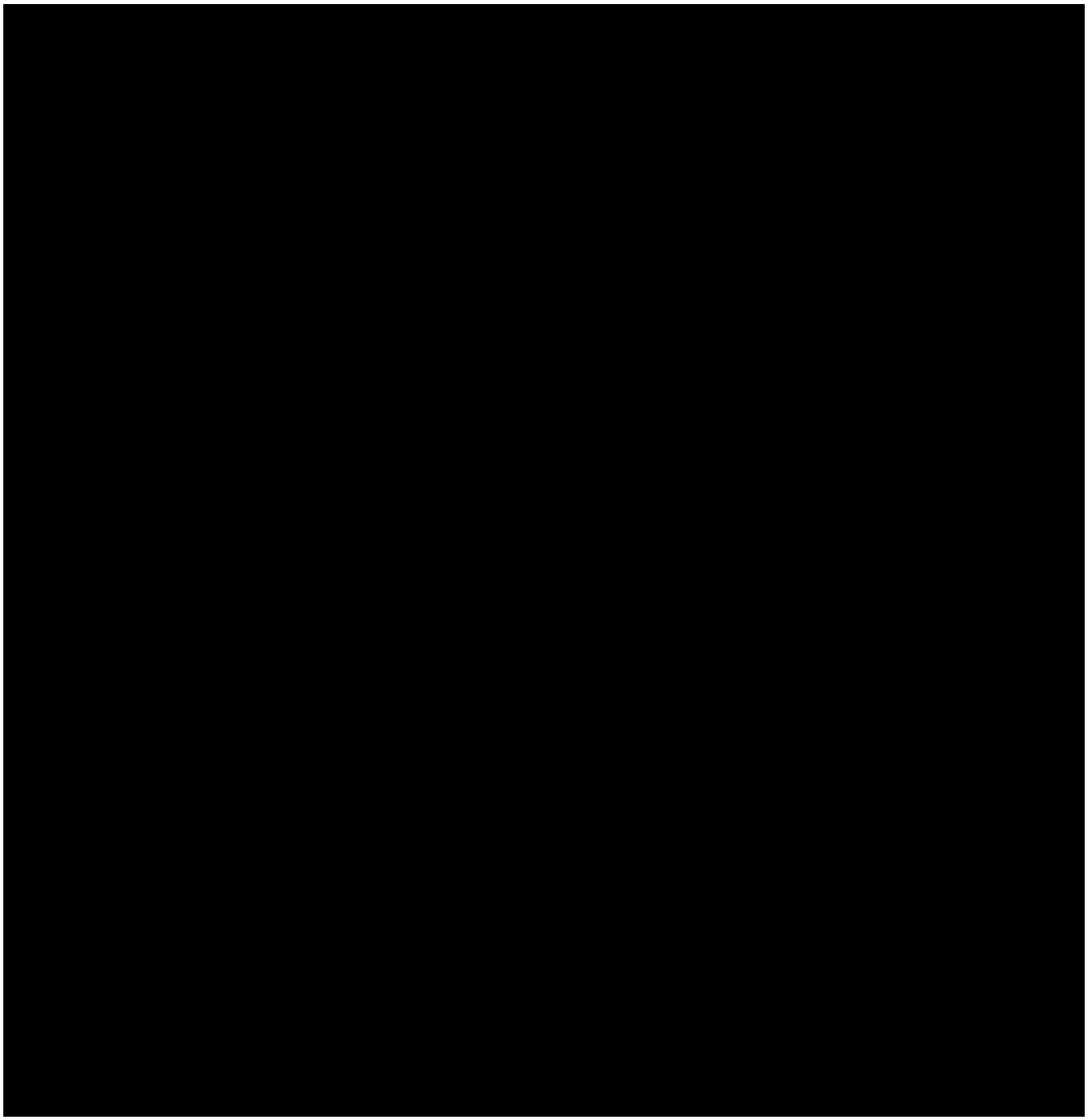
5.1.9. Survival Follow-up Period

After the EoT visit or 28 days after receipt of the last dose of study drug, all participants (including those discontinued during the DLT evaluation period) who have not withdrawn consent, will enter the Survival Follow-up Period and are to be followed up to the end of study for survival by electronic methods (e.g., email, EMR review) or telephone communication every 2 months until the end of study. For the first 2-month follow-up in the Survival Follow up Period, participants will be required to have an in-clinic visit to obtain required assessments unless the subject has initiated a new anti-cancer treatment. Participants should be followed until death, the participant chooses to have an EOS visit, or the study has been completed, even if they have started a new anti-cancer treatment.

5.2. Rationale for STAR0602 Dose Justification

[redacted]





[redacted]

5.2.1.1.3. Justification for Starting Dose of [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] balances a safe starting dose with the need to test pharmacologically relevant and pharmacodynamically detectable doses of STAR0602 in patients with advanced cancer.

Figure 5. Integrated Summary of STAR0602 Pharmacology, MABEL Estimates, and C_{max} Predictions for Phase 1 Dose Escalation



The safety of the proposed starting dose [redacted] mg/kg and the escalation scheme is considered in the context of findings and limits defined in the [redacted]-week GLP toxicology study of IV STAR0602 in cynomolgus monkeys. Table 14 and Table 15 provide dose and exposure margins for the proposed STAR0602 starting dose and dose escalation scheme based on predicted human STAR0602 PK and proposed doses vs. toxicokinetic parameters from [redacted] dose (cycle) of the [redacted]-week GLP toxicology study.

Table 14 Safety Margin Comparisons for Starting Dose Versus GLP Toxicology Dose Limits

[redacted]

Calculated STAR0602 exposure margins using STAR0602 plasma toxicokinetics in monkeys from the [redacted]-week GLP toxicology study and predicted human plasma STAR0602 exposures across the proposed Phase 1 dose escalation are summarized in Table 15.

The predicted human STAR0602 C_{max} ([redacted] and $AUC_{0\text{-}inf}$ [redacted] with a [redacted] than the C_{max}, and $AUCt_{last}$ associated with the [redacted]-week GLP toxicology study in monkeys (Table 15).

Table 15 Safety Margin Comparison of Predicted Human STAR0602 Exposures Versus Monkey Toxicokinetics from [redacted]-week GLP Toxicology Study of IV STAR0602

[redacted]

5.2.1.1.4. Therapeutic Dose Range and IV STAR0602 Dose Escalation Strategy

[redacted]

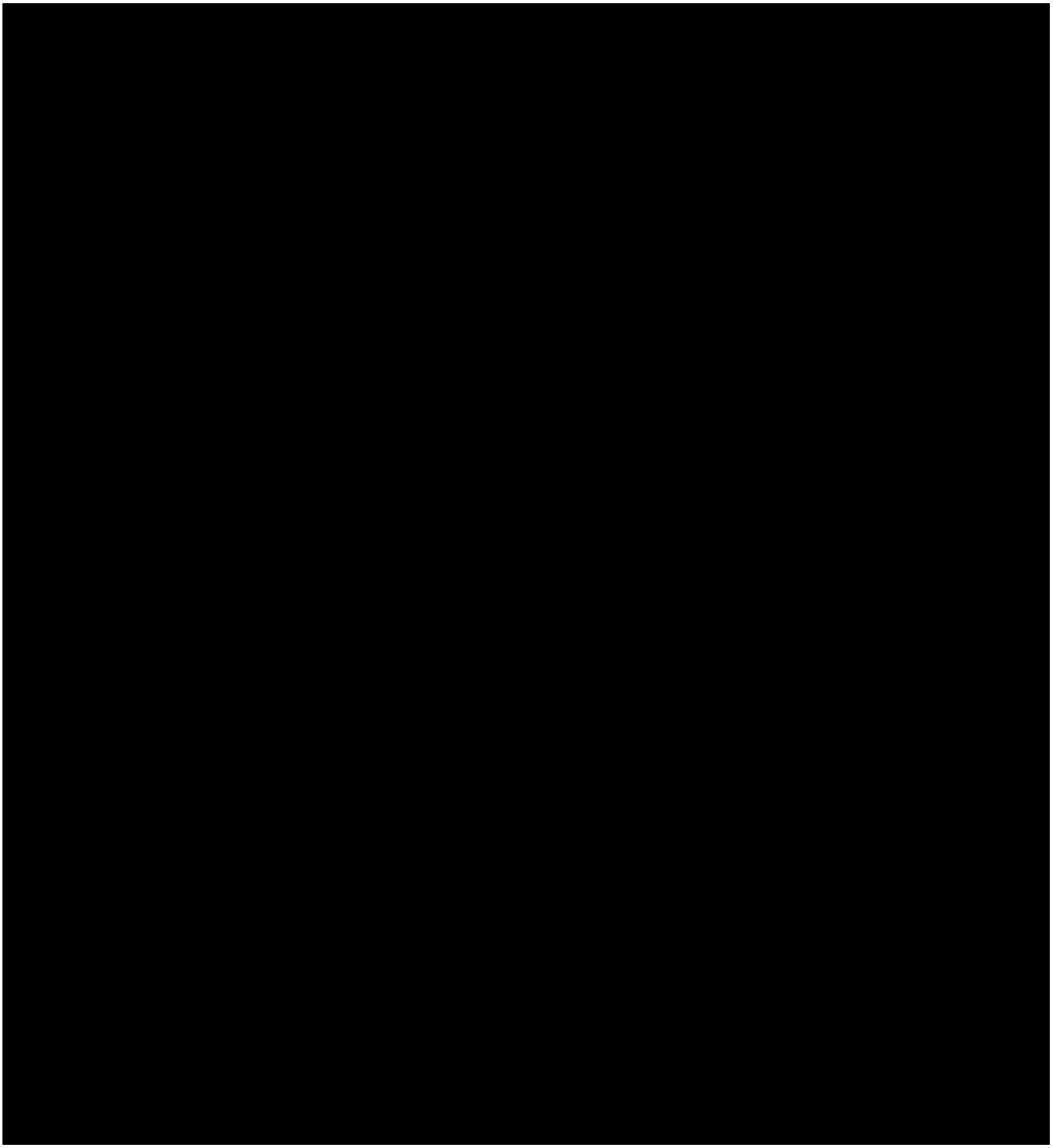
STAR0602 molecules, a target therapeutically effective dose range in humans of [redacted] mg/kg is proposed.

As illustrated in Table 15, the predicted human [redacted] in the Phase 1 dose escalation, unless dose-limiting toxicities (DLTs) or the optimal biological dose (OBD) is reached earlier in the escalation.

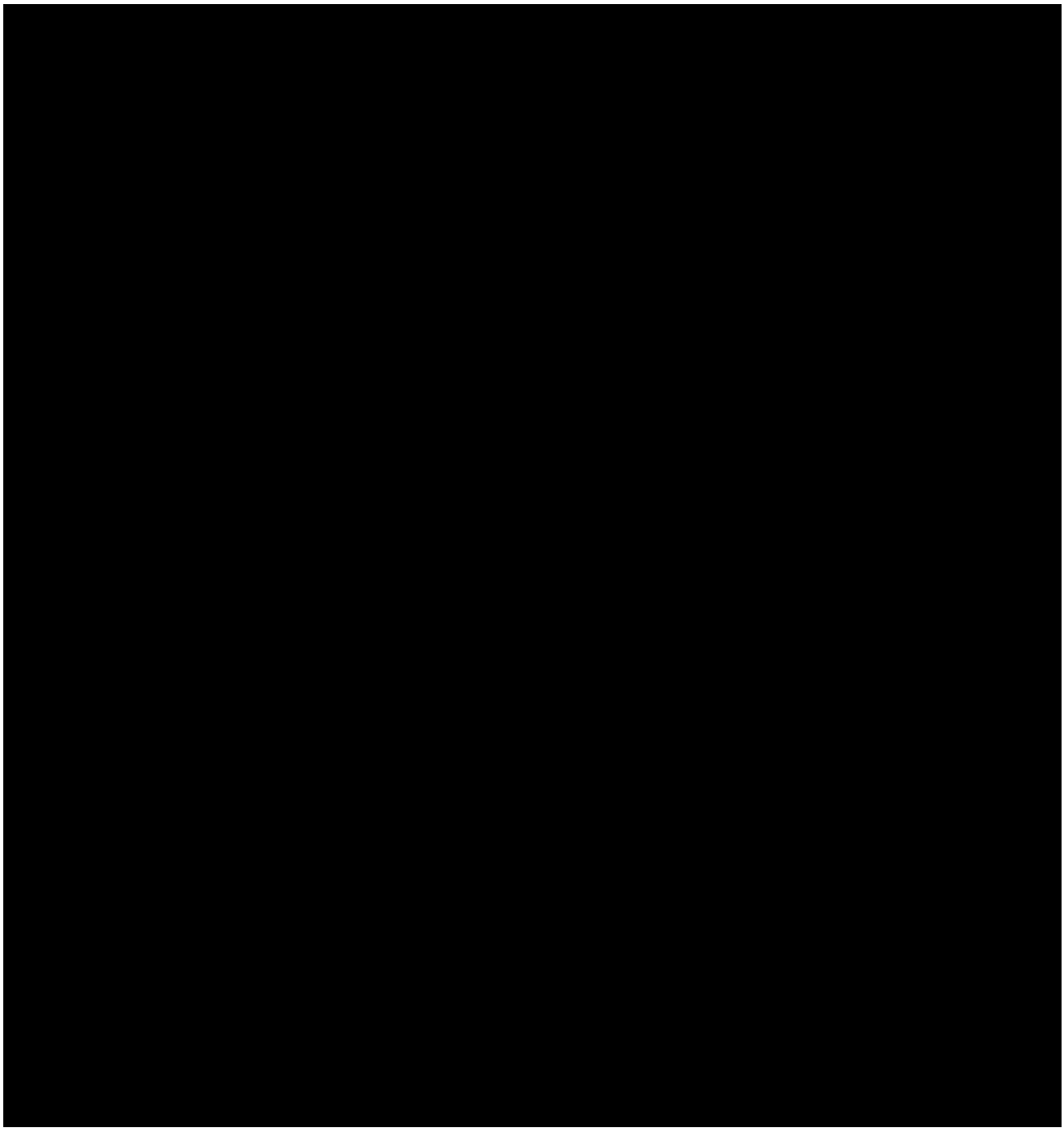
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5.2.2. Step-up Dose Escalation – Phase 1 Group B

[redacted]

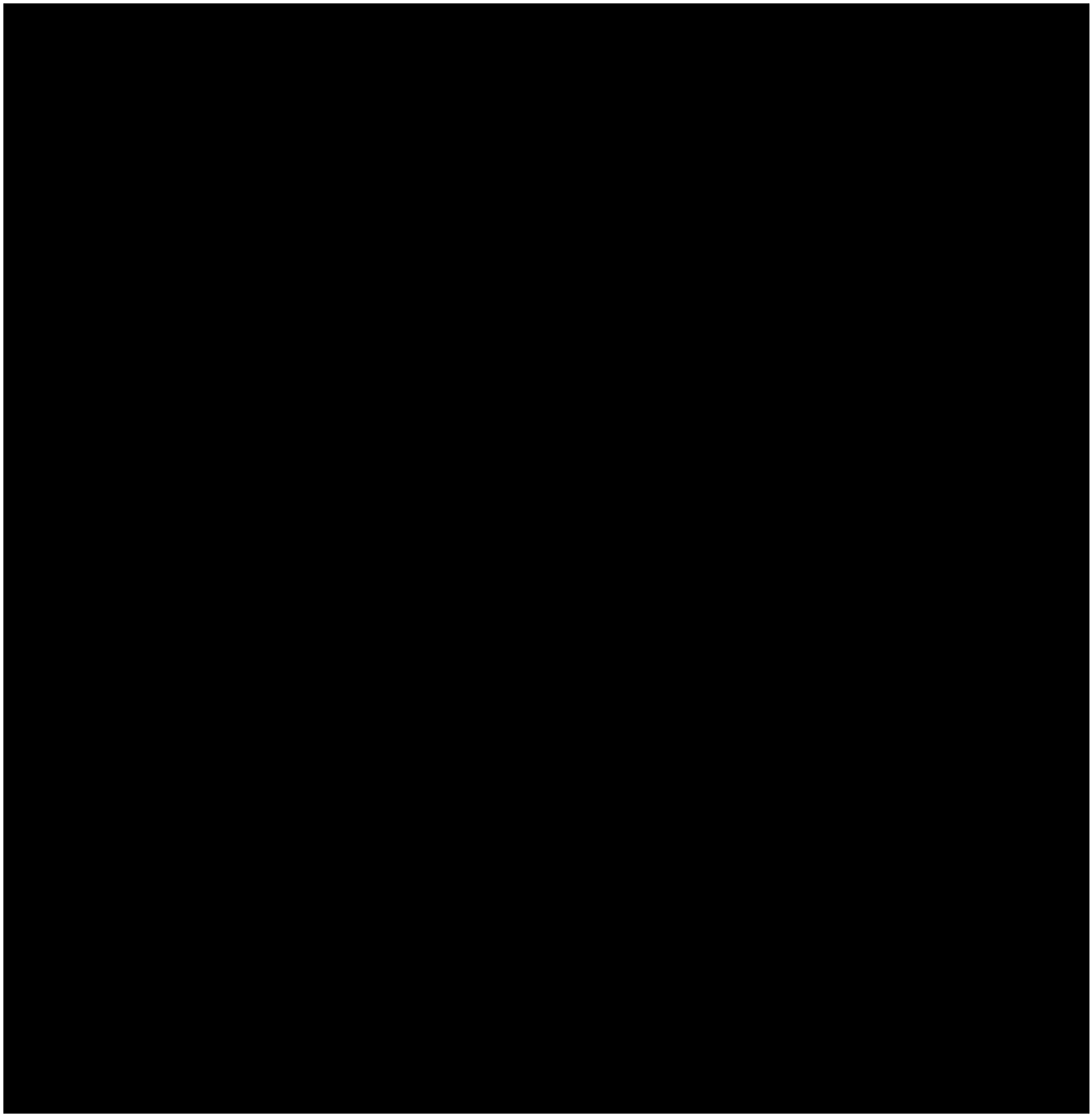




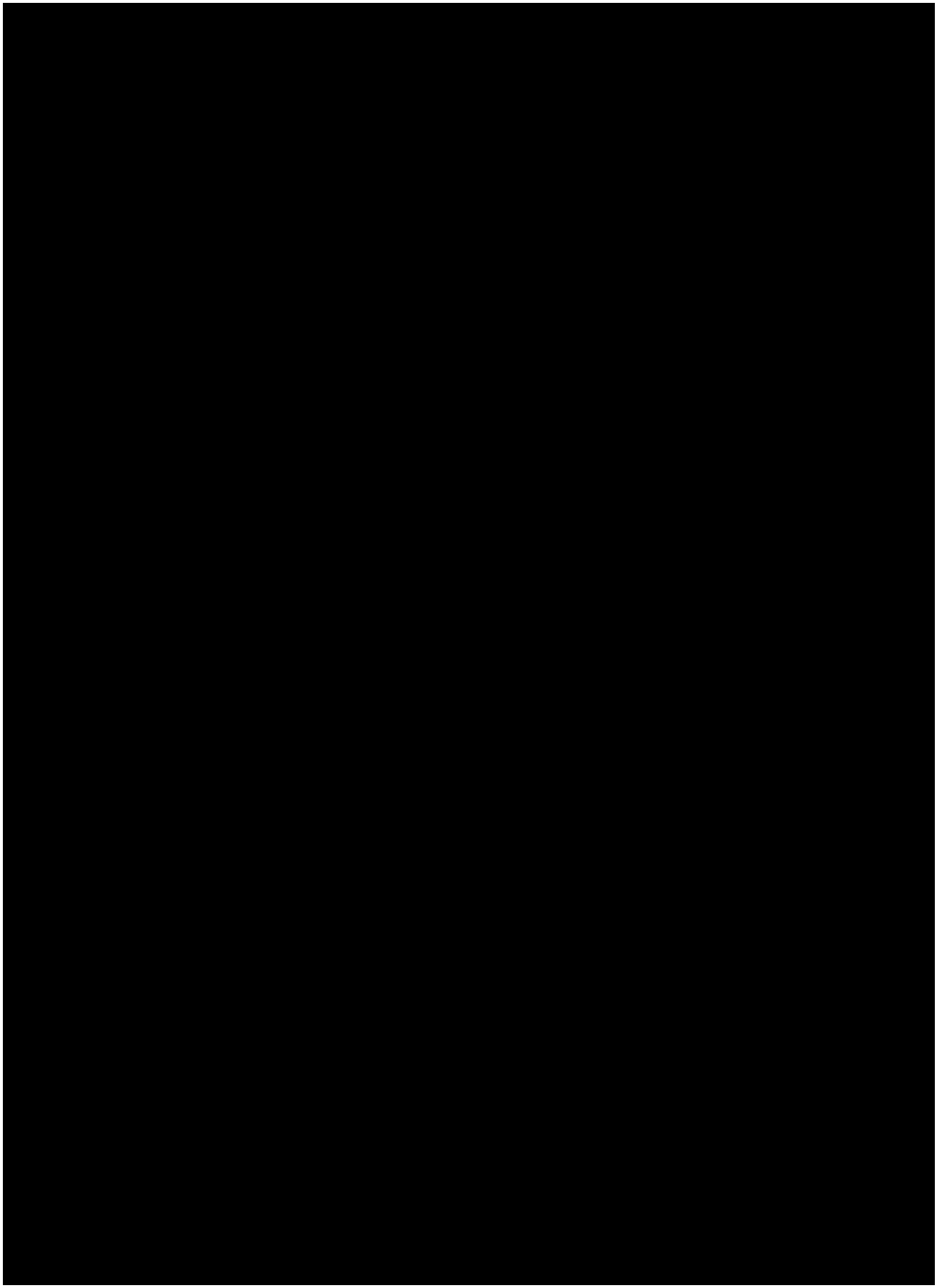








[redacted]



[redacted]

5.3. Study Duration and Dates

Participants will be treated with study drug STAR0602 until disease progression or unacceptable toxicity.

It is expected that enrollment of the Dose Escalation portion of the study, Phase 1, will occur over approximately 15 months, and that enrollment of the Dose Expansion portion of the study, Phase 2 will take approximately 15 months. The total time for conducting this study is expected to be approximately 42 months (including approximately 52 weeks of Survival Follow-up). These estimates of the timing for study conduct may vary from those observed during the actual conduct of the study.

[17] https://products.sanofi.us/taxotere/taxotere.pdf
[18] https://pdf.hres.ca/dpd_pm/00041993.PDF
[19] https://www.medicines.org.uk/emc/product/7206/smpc#gref

6. STUDY POPULATION SELECTION

6.1. Study Population

Participants must have histologically confirmed solid tumors that are unresectable, locally advanced, or metastatic and for which standard curative therapies do not exist or are no longer effective or have intolerable toxicities or patient refusal. Participants should not have received more than three regimens of prior therapies for their advanced or metastatic diseases. For Phase 2 Cohorts 8 and 10 (see below), participants should not have received more than one line of prior therapy.

See Section 5.1.1 and Section 5.1.2 for summaries of participants to be included in Phase 1 and Phase 2, respectively.

6.2. Inclusion Criteria

Each subject must also meet all the following criteria to be enrolled in this study:

General:

1. Age ≥ 18 years old.
2. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 1.
3. Ability to provide written informed consent prior to initiation of any study-related tests or procedures that are not part of standard of care for the participant's disease. Participants must also be willing and able to comply with study procedures, including the acquisition of specified research specimens.
4. Life expectancy ≥ 12 weeks.
5. Measurable disease as per RECIST v1.1 criteria and documented by CT and/or MRI. Cutaneous or subcutaneous lesions must be measurable by calipers. Lesions to be used as measurable disease for the purpose of response assessment must either: a) not reside in a field that has been subjected to prior radiotherapy; or b) have demonstrated clear evidence of radiographic progression since the completion of prior radiotherapy and prior to study enrollment.

Tumor Histology Types

6. For Phase 1, subjects must have one of the following solid tumors:
    1. High mutational burden (TMB-H per local institutional testing); Tumor specimen is preferred (≥ 10 mut/Mb), but if not available, liquid biopsy is allowed;
    (If a patient's TMB is between 9-10 mut/Mb, the patient may be eligible for enrollment upon approval by the Sponsor.)
    2. MSI-H/dMMR cancer (per local institutional testing); Tumor specimen is preferred, but if not available, liquid biopsy is allowed;
    3. Virally associated tumors such as Merkel cell carcinoma, cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancers, or EBV-related solid tumors. No viral testing required for Merkel cell carcinoma, cervical, or anal cancers. For oropharyngeal, penile, vaginal, and vulvar cancers, human papilloma virus (HPV)

positivity documented per local institutional testing is required. For EBV-related solid tumors, EBV positivity documented per local institutional testing is required.

4. Solid tumors generally considered as immunogenic (e.g., melanoma and renal cell carcinoma) are eligible without prior testing for TMB, MSI or viral status after the Sponsor's approval.

7. For Phase 2, participants must have one of the following solid tumors:

    1. High mutational burden (TMB-H ≥ 10 mut/Mb per local site testing). Tumor specimen is preferred, but if not available, liquid biopsy is allowed;
    (If a patient's TMB is between 9-10 mut/Mb, the patient may be eligible for enrollment upon approval by the sponsor.)
    2. MSI-H/dMMR cancer (per local site testing). Tumor specimen is preferred, but if not available, liquid biopsy is allowed;
    3. CRC (both Ras wild-type and mutant) TMB-H, or MSI-H/dMMR, or both TMB-H and MSI-H/dMMR as defined above;
    4. Virally associated tumors such as Merkel cell carcinoma, cervical, oropharyngeal, anal, penile, vaginal, and vulvar cancers, or EBV-related solid tumors. No viral testing required for Merkel cell carcinoma, cervical or anal cancers. For oropharyngeal, penile, vaginal, and vulvar cancers, HPV positivity documented per local institutional testing is required. For EBV-related solid tumors, EBV positivity documented per local institutional testing is required;
    5. Metastatic triple-negative breast cancer (mTNBC);
    6. Platinum-resistant epithelial ovarian cancer;
    7. Metastatic castration-resistant prostate cancer (mCRPC);
    8. [redacted]
    9. Solid tumors generally considered as immunogenic (e.g., melanoma and renal cell carcinoma) are eligible without prior testing for TMB, MSI or viral status after the Sponsor's approval;
    10. [redacted]

a. [redacted];

Other histologies may also be included in Phase 2 as additional data emerge to support their inclusion.

Tumor Specimen:

8. Participants must allow for acquisition of existing formalin-fixed paraffin-embedded [redacted]

[redacted]

[redacted]

Laboratory Features:

10. **Acceptable laboratory parameters as follows:**

- Albumin ≥ 3.0 g/dL;
- Platelet count ≥ 75 × 10^3/µL;
- Hemoglobin ≥ 8.5 g/dL;
- Absolute neutrophil count (ANC) ≥ 1.5 × 10^3/µL (participants with duffy-null phenotype who have baseline ANC lower than this criterion may be enrolled upon the approval by the Sponsor);
- ALT/AST ≤ 3.0 x upper limit of normal (ULN); ≤ 5.0 X ULN with hepatic metastases; Phase 2 Cohort 8, ≤ 1.5 ULN)
- Total bilirubin ≤ 1.5 × ULN (Phase 2 Cohort 8 < ULN), except participants with Gilbert's syndrome, who may be enrolled if the conjugated bilirubin is within normal limits or approved by the Sponsor.
- Calculated creatinine clearance ≥ 50 mL/min (based on Cockcroft-Gault formula (Appendix 6) or on a 24-hour urine collection). For over- or under- weight participants, ideal body weight should be used for calculating the creatinine clearance.

Reproductive Features (see Appendix 5 for contraception requirements):

11. Female participants of childbearing potential (not surgically sterilized and between menarche and 1-year post-menopause) must have a negative serum (screening) or urine pregnancy test performed within 72 hours prior to the initiation of study drug administration. Female participants of childbearing potential must be willing to use a condom plus 1 of the highly effective methods of contraception throughout the study, from the time of consent through 60 days after the last dose of STAR0602. Examples of effective contraception are birth control pills, birth control patch (e.g., Ortho Evra), NuvaRing, intrauterine device, female condom, diaphragm with spermicide, cervical cap, use of a condom by the sexual partner, documented sterile sexual partner or documented evidence of surgical sterilization (e.g., tubal ligation or hysterectomy) at least 6 months prior to Screening. Abstinence is acceptable if this is the established and the preferred contraception method for the subject. It is not necessary to use any other method of contraception when complete abstinence is elected.
12. Male participants with partners of childbearing potential must use barrier contraception from the time of consent through 60 days after last dose of STAR0602 and must not donate sperm during this period. In addition, male participants should also have their partners use contraception (as documented for female participants) for the same period of time.

CNS Metastases:

13. Symptomatic central nervous system (CNS) metastases must have been treated, be asymptomatic for ≥ 14 days, and meet the following at the time of enrollment:
    - No concurrent treatment for CNS disease (e.g., surgery, radiation, corticosteroids > 10 mg prednisone/day or equivalent);
    - No concurrent leptomeningeal disease or cord compression.

Previous Checkpoint Inhibitor Therapy:

14. Participants who have previously received a CPI (e.g., anti-PD-L1, anti-PD-1, anti-CTLA-4) prior to enrollment must have CPI immune-related toxicity resolved to either Grade ≤ 1 or baseline (prior to the CPI) to be eligible for enrollment.
    - Participants who experienced previous CPI-related endocrine abnormalities are eligible for the study regardless of CTCAE grade if well controlled on replacement therapy.
    - Participants who have had previous CPI-related Grade 3 to 4 pneumonitis, peri/myocarditis, colitis and bowel perforation, myositis, encephalitis, or peripheral neuropathy need to be discussed with and approved by the Sponsor and Medical Monitor.

6.3. Exclusion Criteria

Participants who meet any of the following criteria will be excluded from the study:

1. Participants with a history of known autoimmune disease with exceptions of:
    - Vitiligo;
    - Psoriasis, atopic dermatitis, or other autoimmune skin condition not requiring systemic treatment;
    - History of Graves' disease, now euthyroid for > 4 weeks;
    - Hypothyroidism managed by thyroid replacement;
    - Alopecia;
    - Arthritis managed without systemic therapy beyond oral nonsteroidal anti-inflammatory drugs.
    - Adrenal insufficiency- well controlled on replacement therapy.
2. Major surgery or traumatic injury within 8 weeks before first dose of study drug.
3. Unhealed wounds from surgery or injury.
4. Treatment with >10 mg per day of prednisone (or equivalent) or other immune-suppressive drugs within 7 days prior to the initiation of study drug. Exceptions may be made for patients who have had allergic reaction to iodinated contrast media. Steroids for topical, ophthalmic, inhaled, or nasal administration are allowed.
5. Prior therapy within the following timeframe before the planned infusion of STAR0602 as follows:

- Cytotoxic chemotherapy, small molecule inhibitors, radiation, interventional radiology procedure, or similar investigational therapies within ≤ 2 weeks or participants who have not recovered (i.e., ≤ Grade 1 or to baseline) from AEs due to a previously administered agent;
- Monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or similar investigational therapies within 4 weeks prior to the initiation of study drug or participants who have not recovered (i.e., ≤ Grade 1 or to baseline) from AEs due to agents administered more than 4 weeks earlier.

  Note: Participants with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

  Note: Concurrent use of hormones either to maintain castrate levels of testosterone in participants with castration-sensitive prostate cancer or for non-cancer-related conditions (e.g., insulin for diabetes, hormone replacement therapy) is acceptable. Bisphosphonates are permitted for supportive care of bone metastases (e.g., breast or prostate cancer).

6. Clinically significant cardiovascular/vascular disease including:
   - Myocardial infarction or unstable angina < 6 months prior to the initiation of study drug;
   - Clinically significant cardiac arrhythmia (e.g., with potential for hemodynamic instability) not controlled or unresponsive to treatment;
   - Uncontrolled hypertension: systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg; Participants with systolic blood pressure > 140 mmHg but < 180 mmHg and/or diastolic blood pressure > 90 mmHg but < 100 mmHg may be enrolled upon reviewing co-morbidities/risks and after the sponsor approval. These participants need to be closely monitored with their blood pressure assessed and managed at each visit on treatment;
   - Pulmonary embolism, stroke, or transient ischemic attack < 6 months prior to initiation of STAR0602;
   - QTcF (Fridericia correction) prolongation > 480 msec;
   - Congestive heart failure (New York Heart Association Class III-IV);
   - Pericarditis/clinically significant pericardial effusion;
   - Myocarditis;
   - Vasculitis that has not resolved within 6 months prior to study drug.
7. Clinically significant gastrointestinal disorders including:
   - Gastrointestinal perforation < 6 months prior to study drug administration. Participants must have documented evidence (e.g., upper endoscopy, colonoscopy) of completely healed area of prior perforation;

- Gastrointestinal bleeding < 2 months prior to study drug administration. Participants must have documented evidence (e.g., upper endoscopy, colonoscopy) of completely healed area of prior bleeding;
- Pancreatitis <6 months prior to the initiation of study drug. Participants must have a CT scan negative for evidence of remaining disease or normal pancreatic enzyme levels for > 4 weeks prior to the initiation of study drug;
- Diverticulitis flare < 2 months prior to study drug administration. Participants must have a CT scan negative for evidence of remaining disease prior to the initiation of study drug;
- History of Crohn's disease or ulcerative colitis.

8. Inflammatory process that has not resolved for ≥ 4 weeks from the date of first study dose. Participants with chronic low-grade inflammatory processes such as radiation-induced pneumonitis are excluded regardless of duration.
9. Clinically significant pulmonary compromise (e.g., requirement for supplemental oxygen on a continuous basis).
10. Active viral, bacterial, or systemic fungal infection requiring parenteral treatment within 7 days prior to the initiation of study drug. Systemic antiviral, antifungal, or antibacterial therapy must be completed > 1 week prior to the initiation of study drug. Antimicrobial prophylaxis (e.g., for pneumocystis carinii infection) may continue the antimicrobial for that purpose.
11. Vaccination with any live virus vaccine within 4 weeks prior to the initiation of study drug administration. Inactivated annual influenza vaccination is allowed.
12. Participants who are known to be human immunodeficiency virus (HIV) positive or hepatitis B or C positive and have uncontrolled disease. Participants treated for hepatitis C must have viral titers below the limit of quantification. to be eligible. [redacted]
13. Second primary invasive malignancy not in remission for ≥ 1 year. Exceptions include non-melanoma locally advanced skin cancer, cervical carcinoma in situ, localized prostate cancer (Gleason score ≤ 7), resected melanoma in situ, or any malignancy considered to be indolent and never required systemic therapy, with the exception of indolent lymphomas.
14. Any serious underlying medical or psychiatric condition that would preclude understanding and rendering of informed consent or impair the ability of the subject to receive or tolerate the planned treatment.
15. Known hypersensitivity to STAR0602 or any excipient [redacted]) contained in the drug or diluent formulation.

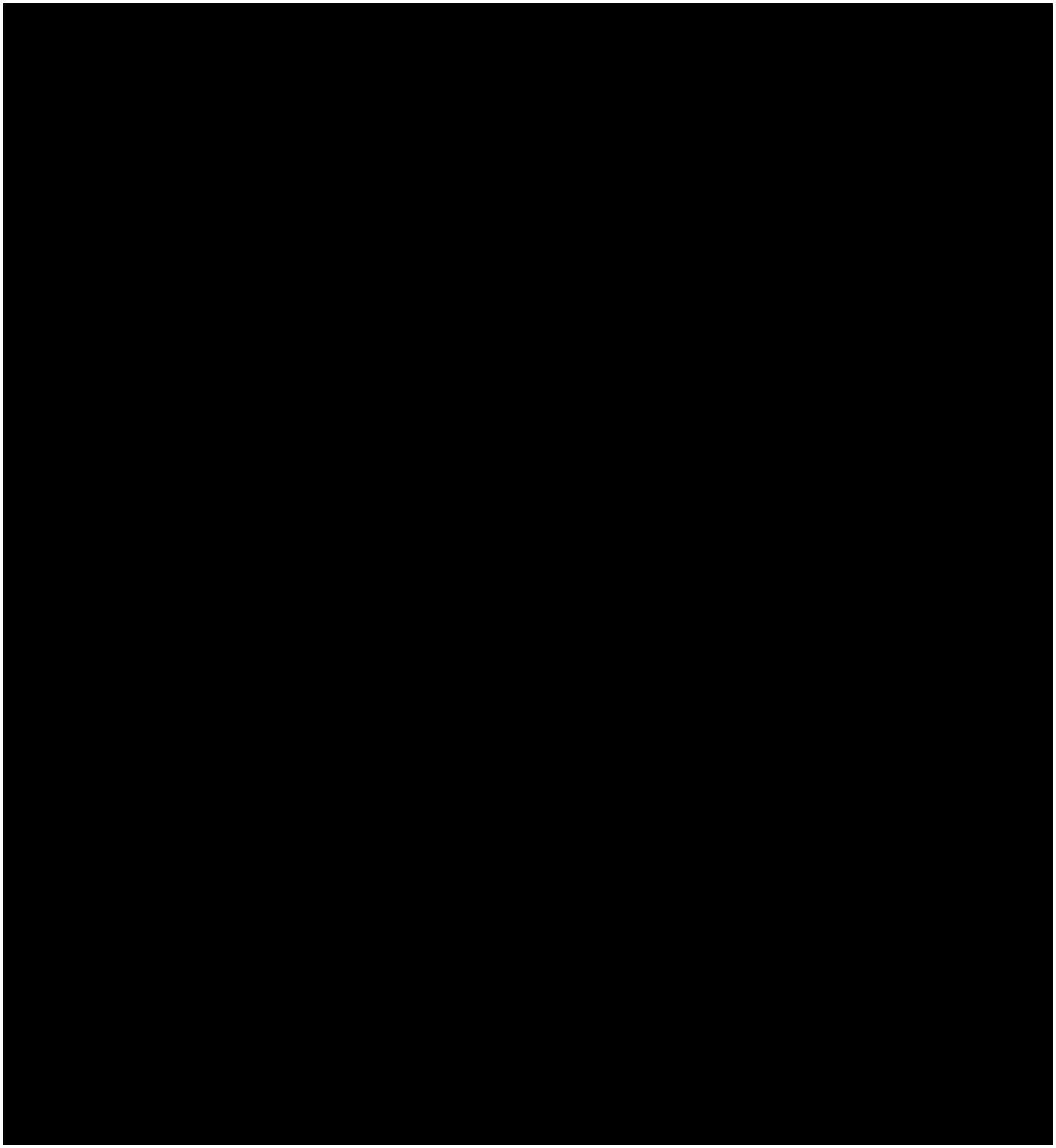
16. Any medical (e.g., requirement of an indwelling catheter such as PleurX or Tenckhoff catheter) or non-medical issue that would contraindicate the participant's participation in the study or confound the results of the study.
17. Pregnant, likely to become pregnant, or lactating women (where pregnancy is defined as the state of a female after conception and until the termination of gestation).
18. [redacted]

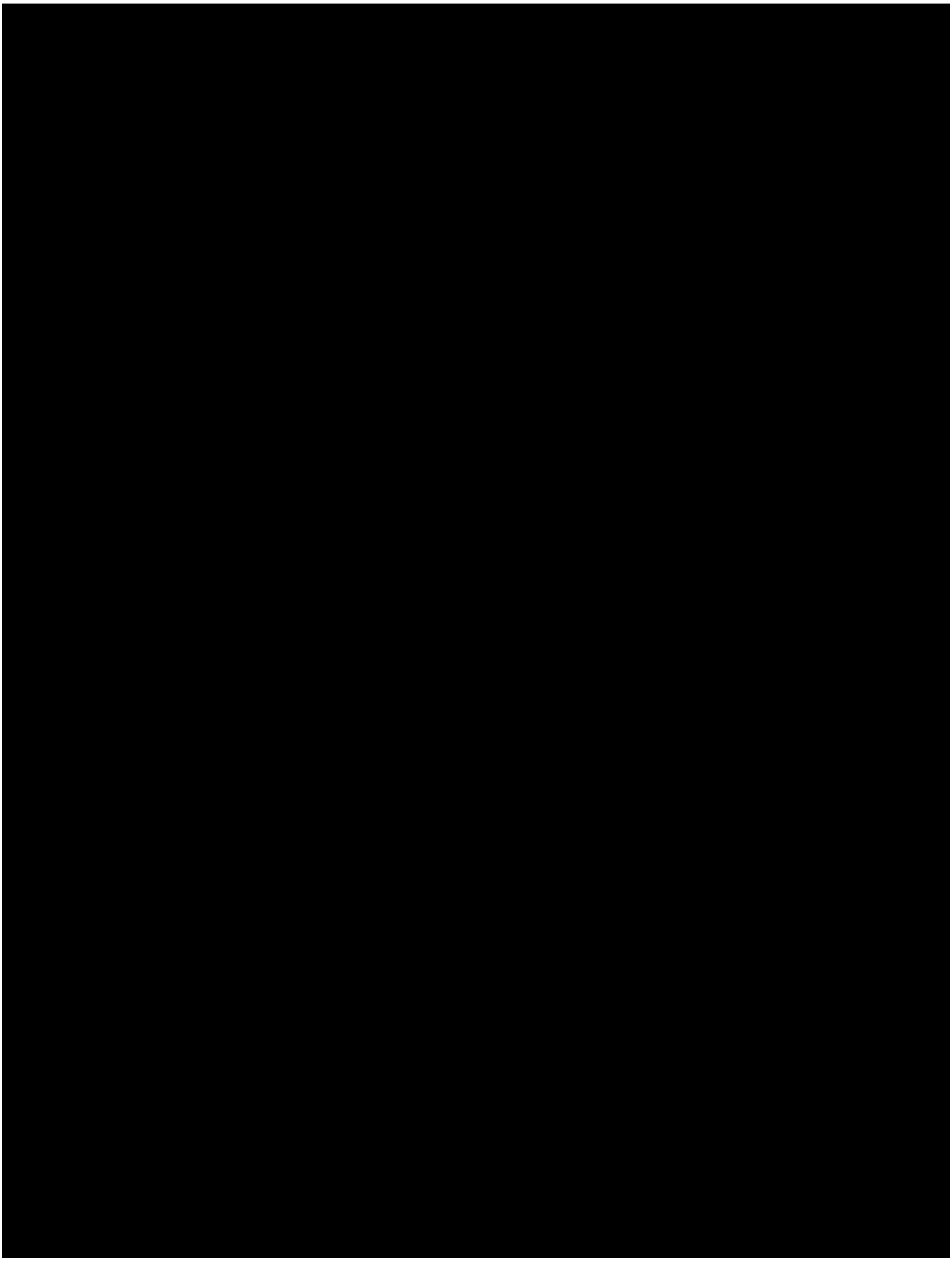
7. STUDY TREATMENT

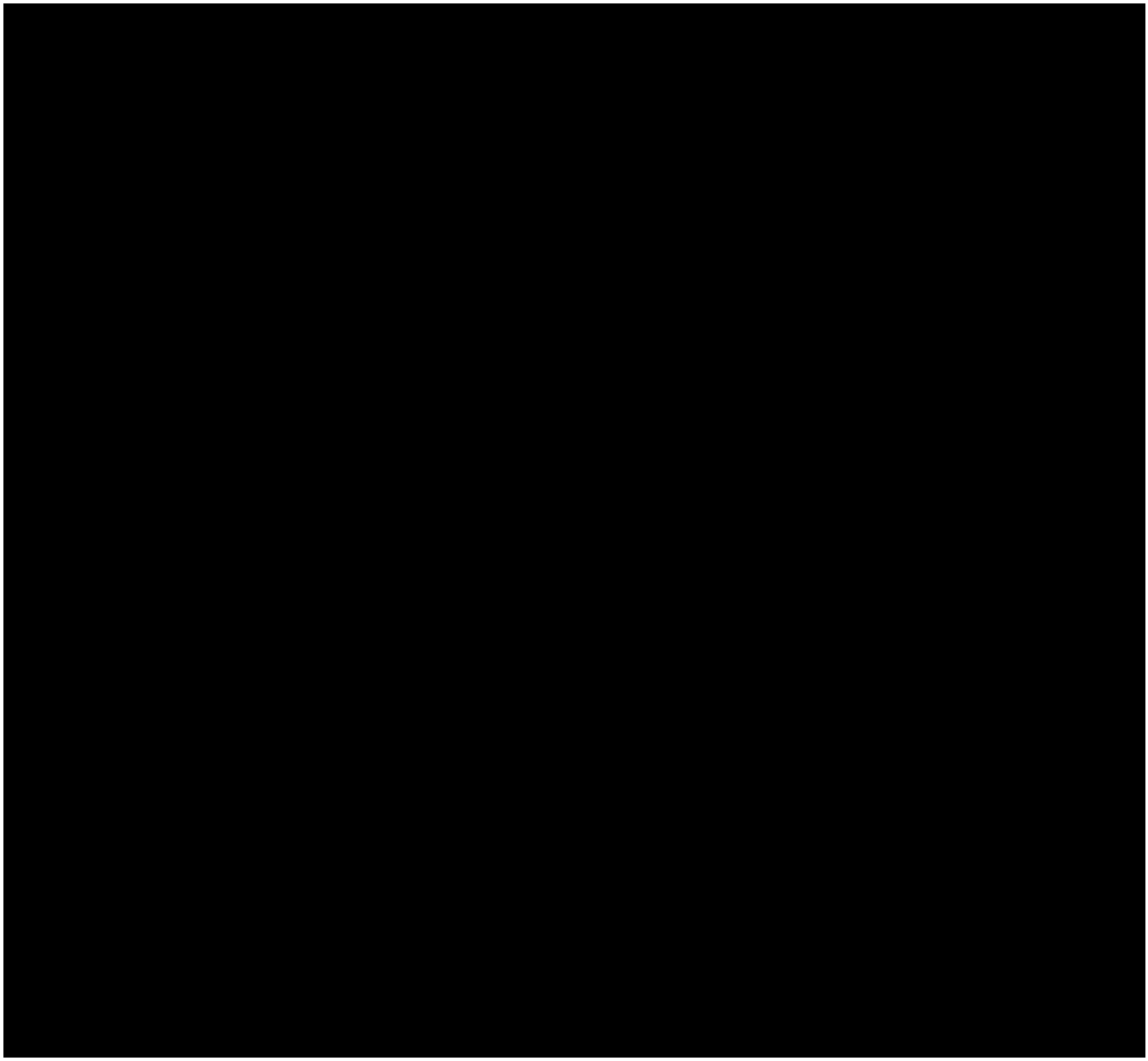
7.1. Description of Treatment

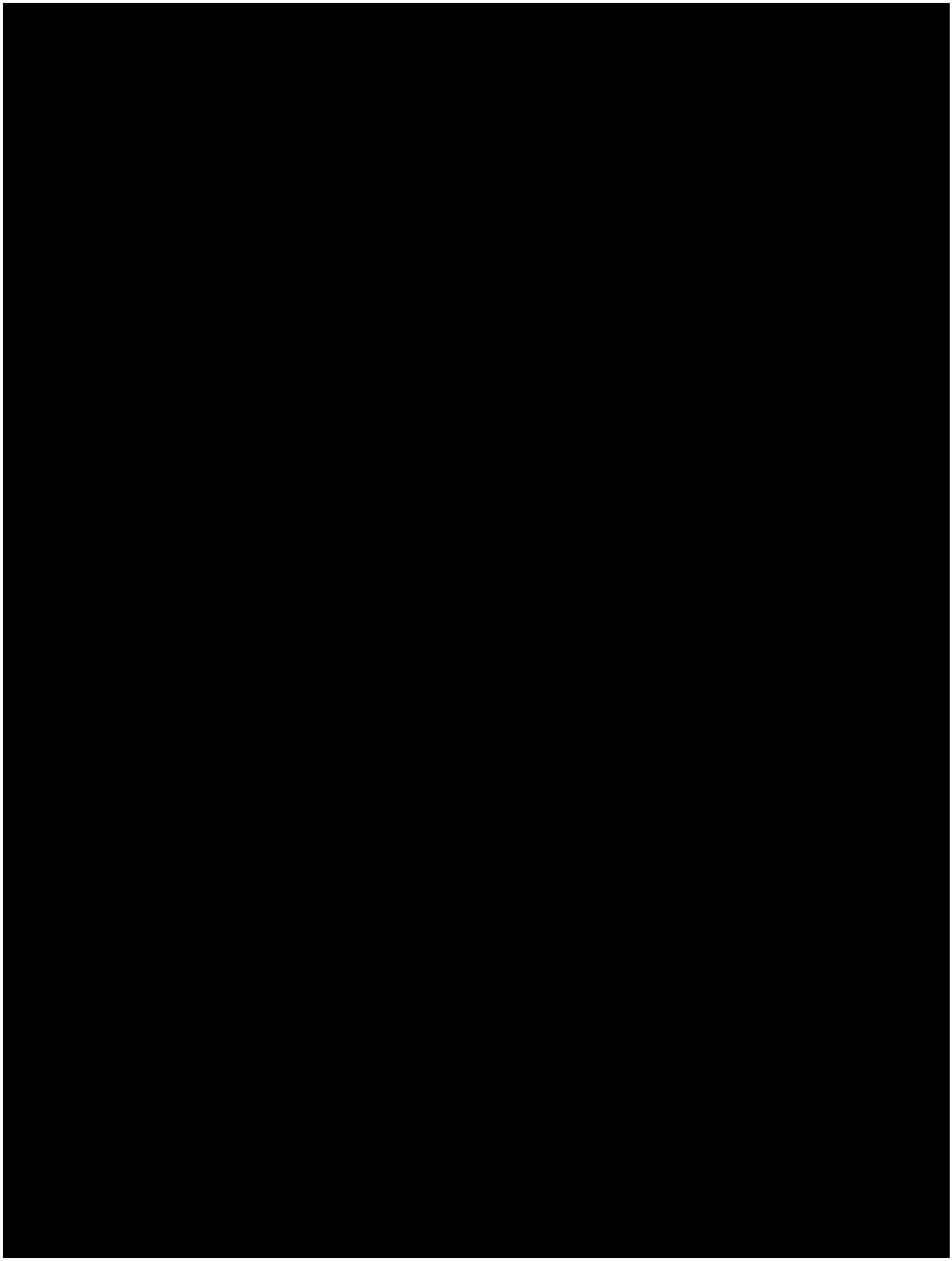
7.1.1. Study Drug

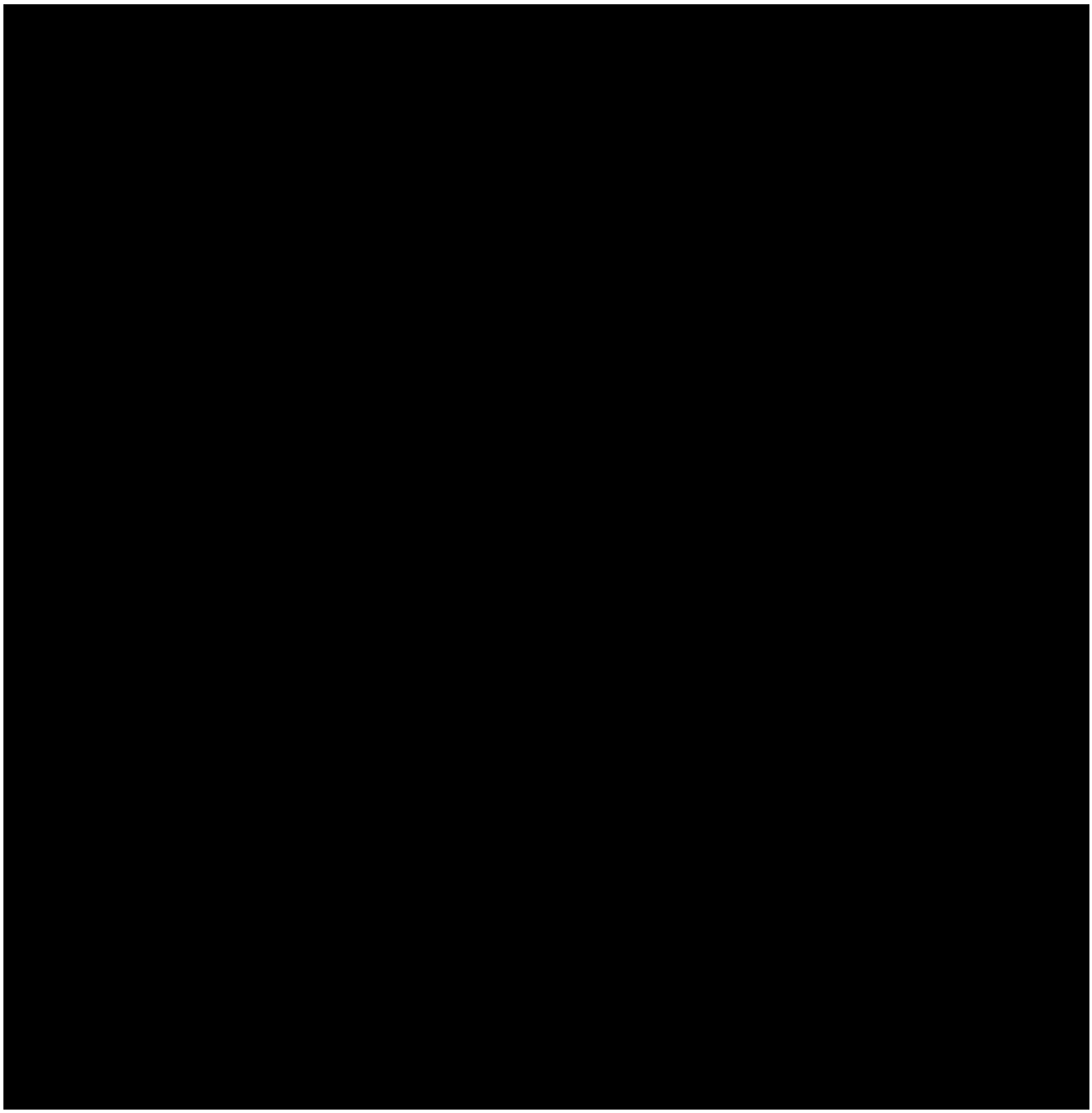
The investigational product (IP) for this study is summarized in Table 16 and will all be open-label administrations.



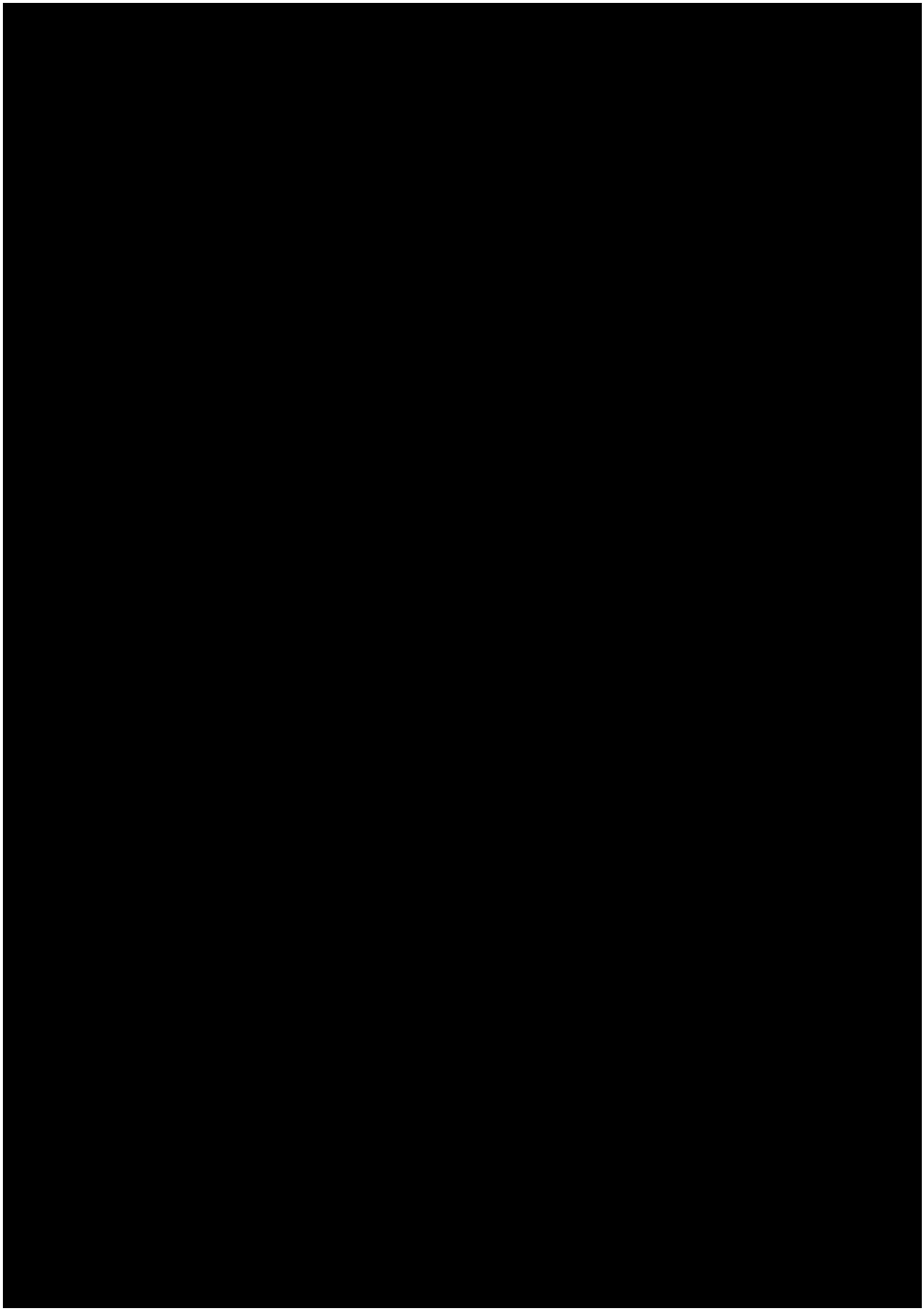


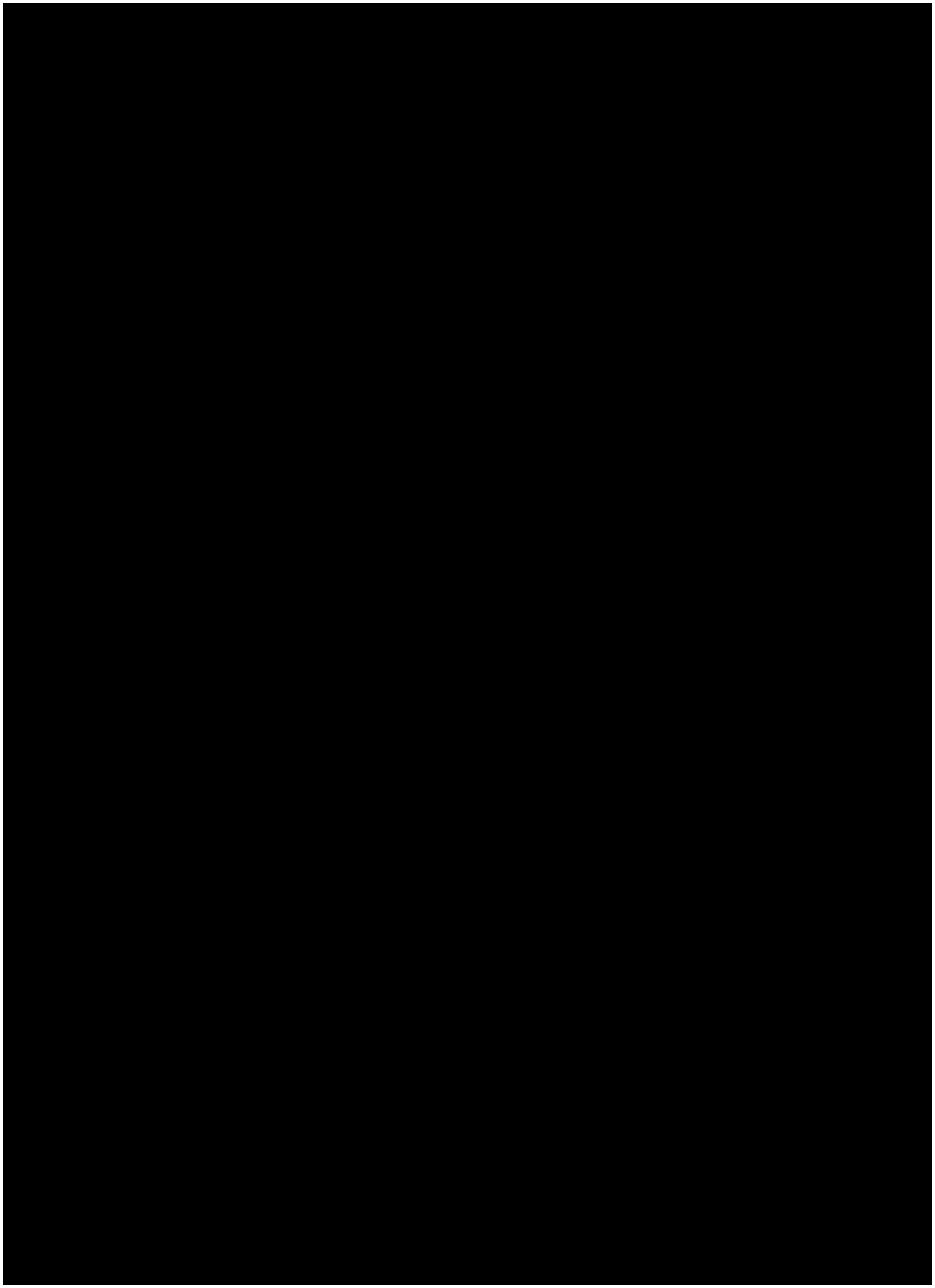


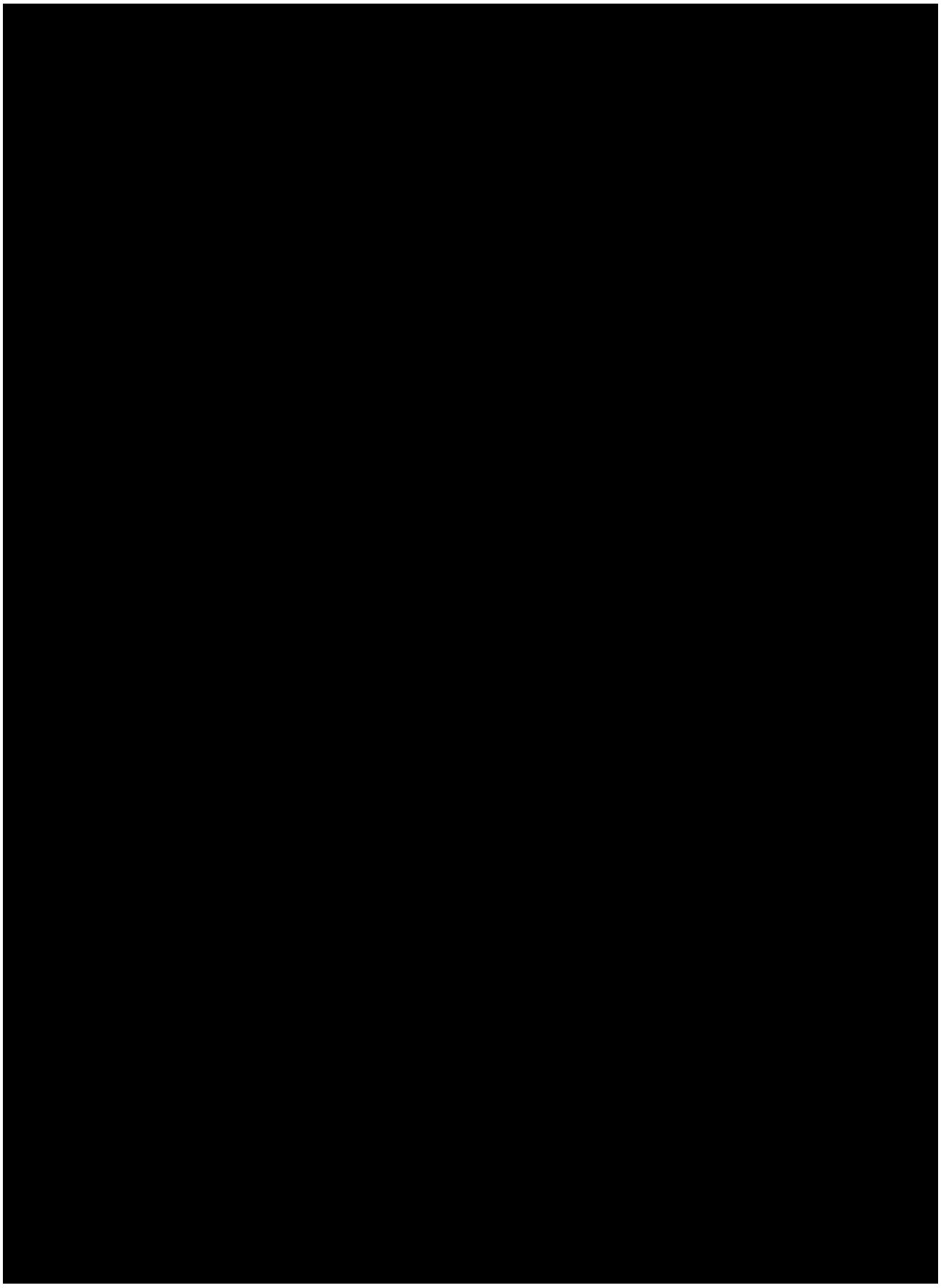


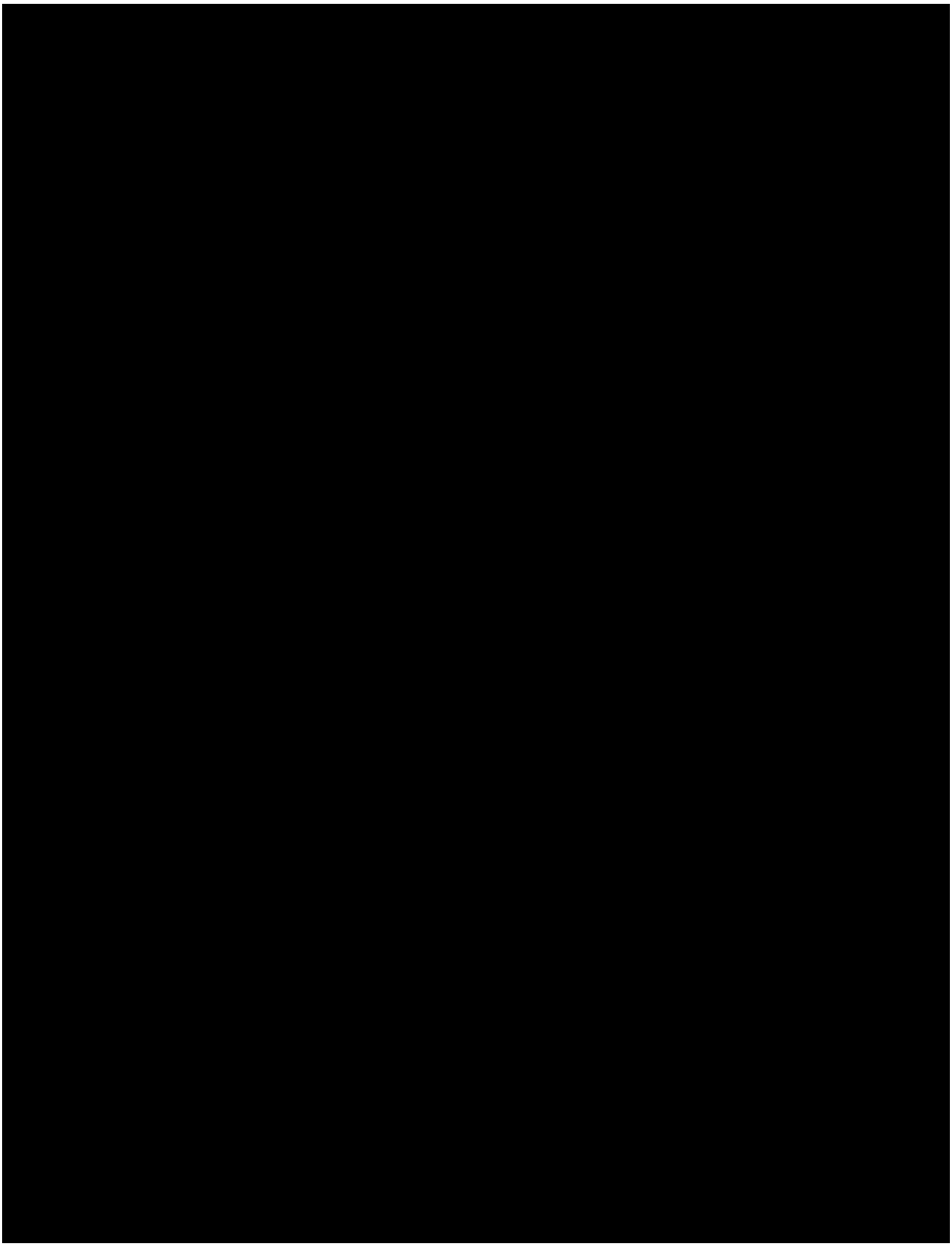


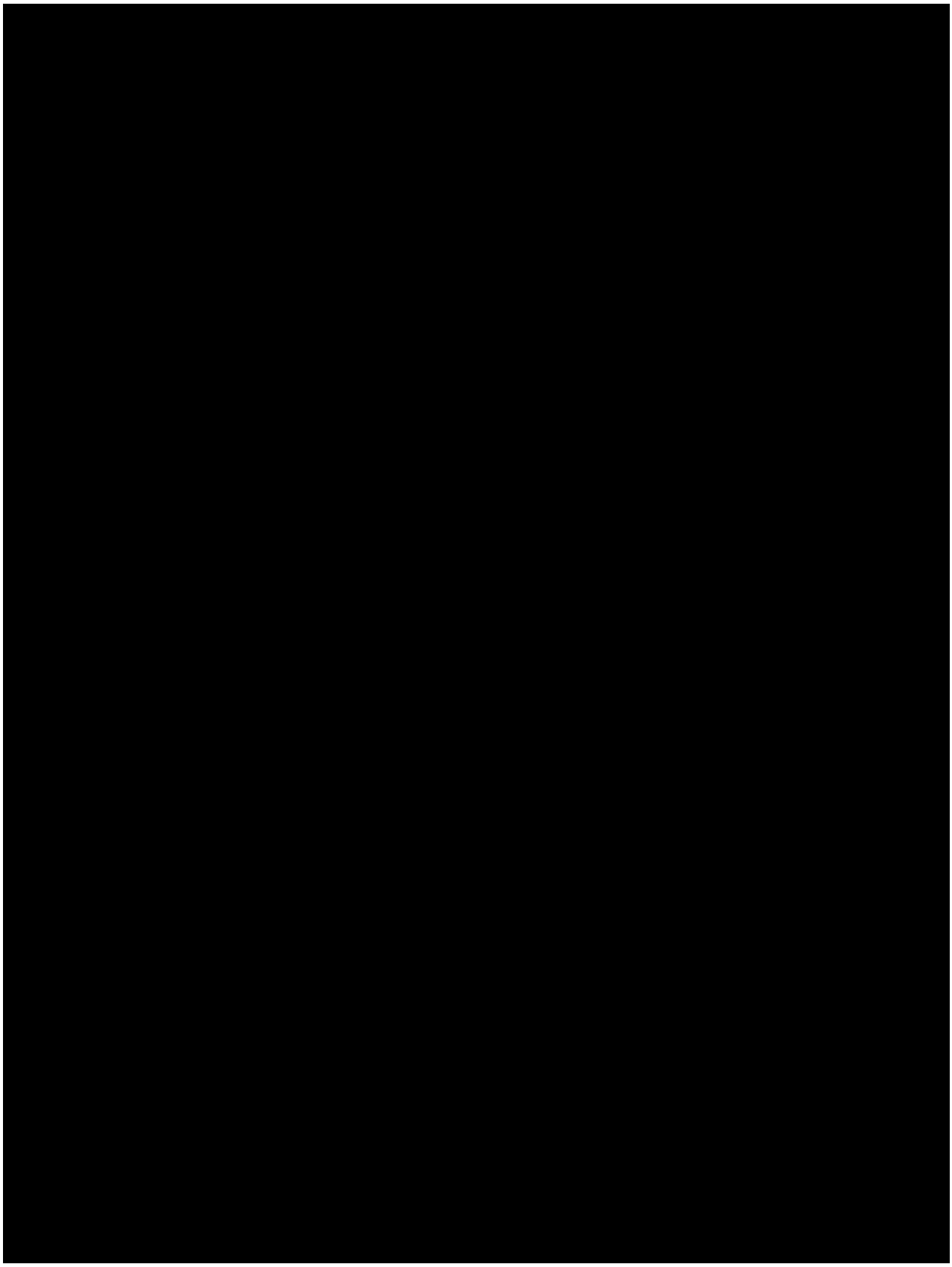


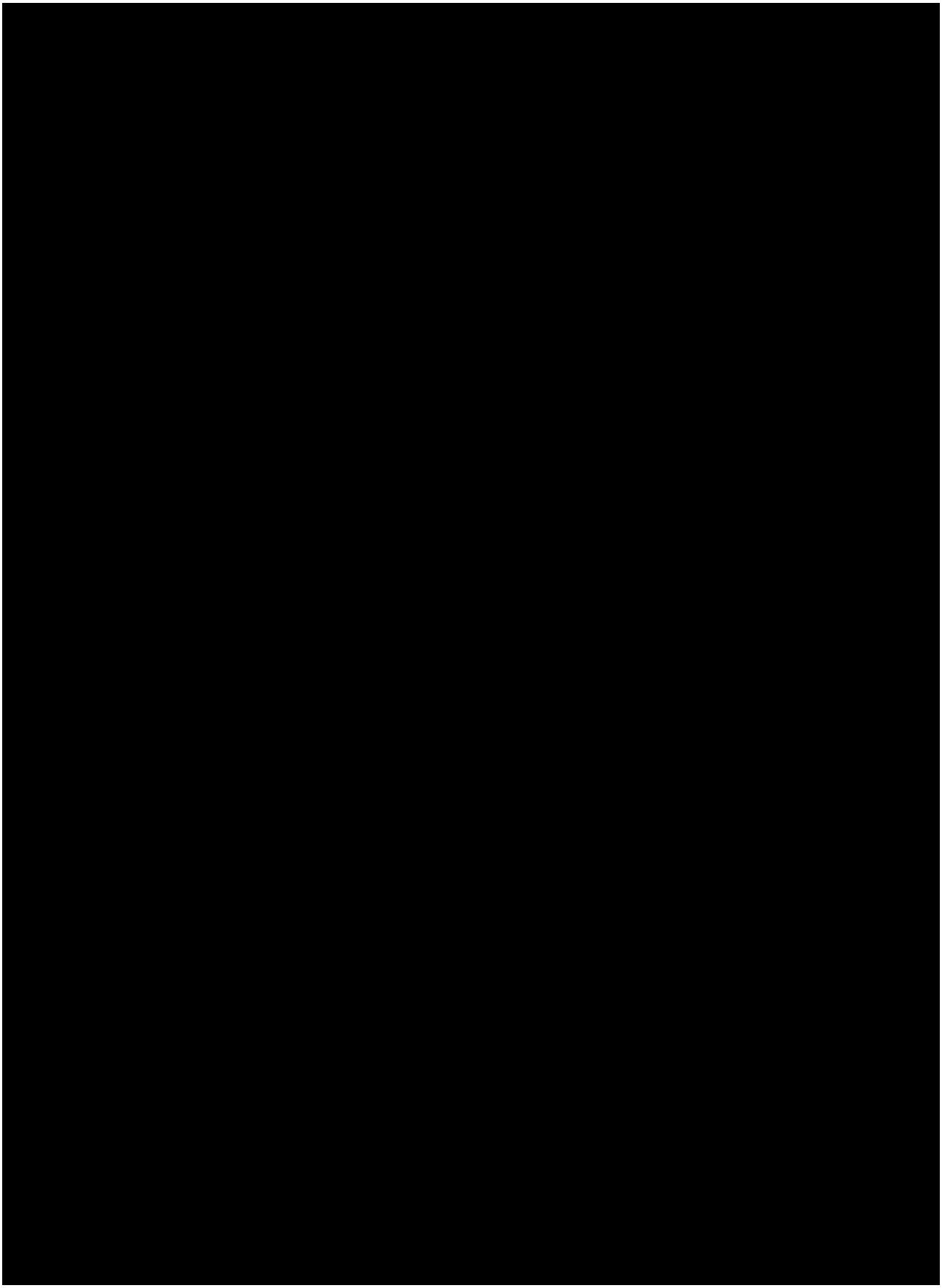




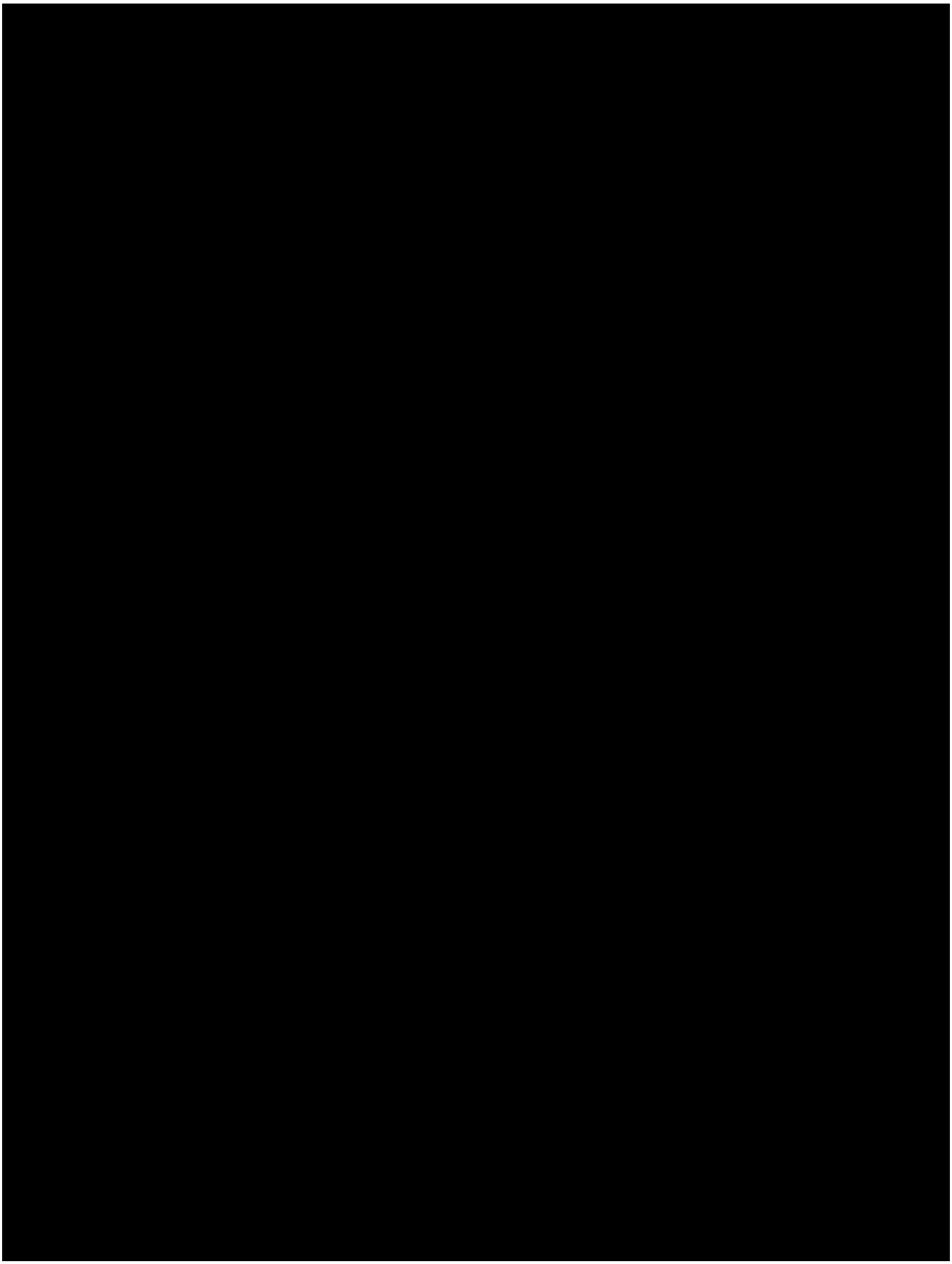


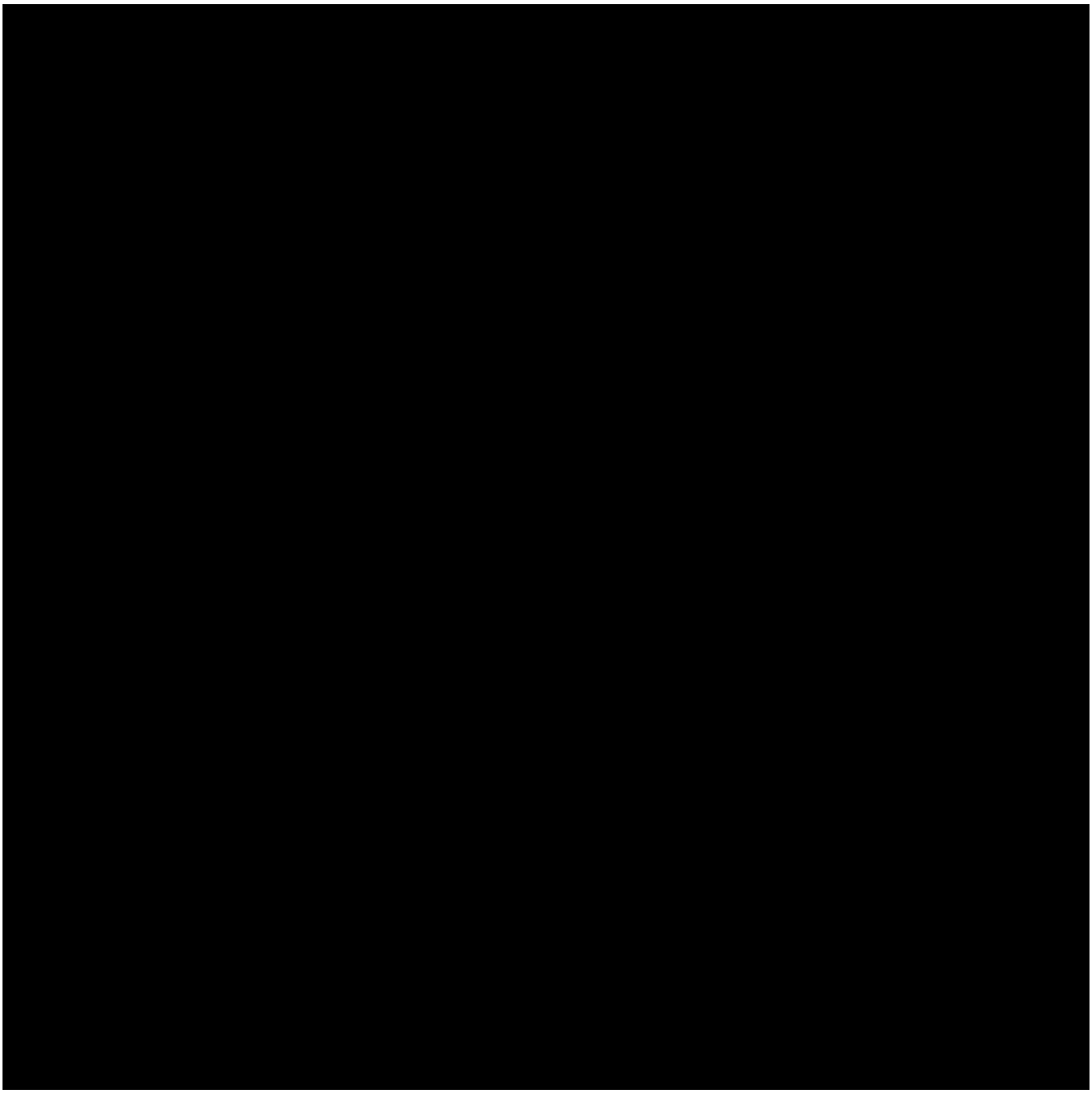












7.3.6. Infusion Reaction Treatment Guidelines

Infusion reaction treatment guidelines are provided in Table 20.

Table 20 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1: Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator.	None
Grade 2: Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	**Stop infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise, dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.	Subject may be premedicated 30-45 minutes) prior to infusion of STAR0602 with: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg PO (or equivalent dose of antipyretic).
Grades 3 or 4 **Grade 3**: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) **Grade 4**: Life-threatening; pressor, or ventilatory support indicated	**Stop infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Vasopressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the Investigator. Hospitalization may be indicated. **Discuss with the Sponsor regarding further trial treatment administration.**	No subsequent dosing

Abbreviations: IV=intravenous; NSAID=Non-steroidal anti-inflammatory drugs; PO=taken by mouth

Sources: Adapted from Rombouts et al, 2020; Roselló et al, 2017

7.3.7. Treatment After Radiologic Progression of Disease

If a subject has initial radiologic progression while waiting the repeat imaging for confirmation per iRECIST, or has confirmed progressive disease (PD) (i.e., 2 scans at least 28 days apart demonstrating PD), the subject may continue STAR0602 treatment if all the following criteria are met and, if in the opinion of the Investigator, the subject will continue to receive benefit from treatment:

[redacted]

7.3.8. Intervention After the End of the Study

During this study, participants will continue treatment with STAR0602 until disease progression or unacceptable toxicity. However, no intervention will be provided to study participants after the end of the study.

7.4. Method of Assigning Participants to Treatment Groups

This is a single-arm study and is not randomized; treatment group assignment is not applicable. Participants will receive STAR0602 as monotherapy or its combination with either docetaxel or irinotecan.

Eligible participants will be enrolled and assigned to the phase of the study that is active at the time of enrollment. Participants in Phase 1 will be assigned to the dosing cohort that is active at time of enrollment (if the current dose level is fully accrued, newly identified participants who meet eligibility criteria may be enrolled into a lower dose level cohort which has already cleared the DLT window, following confirmation by the Sponsor and Medical Monitor. These participants will be termed “expanded enrollment participants”).

7.4.1. Blinding

This trial is open-label for Phase 1 and Phase 2. Treatment assignments are not blinded.

7.5. Concomitant Therapy

Concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements. Concomitant medications will be recorded in the electronic case report form (eCRF). If participants receive prohibited or restricted treatments, as indicated in Section 7.5.2, they will be recorded in the eCRF and will include the start date, name of medication or treatment, dose, unit, route, and frequency. All concomitant medications are to be collected through the EOT visit or until 28 days after the last dose.

The Medical Monitor or Sponsor representative will be consulted for the evaluation of concomitant medications.

7.5.1. Permitted Treatments

Concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed in general. Examples include anti-diarrheal medications, anti-emetics, or electrolyte supplementation. Participants must be told to notify the

investigational site staff about any new medications, herbal remedies, or dietary supplements that he or she takes after the start of the study drug, regardless of treatment duration. All concomitant medications and significant non-drug therapies (including physical therapy, herbal or natural medications, and blood transfusions) administered during the study must be listed on the concomitant medications or the surgical and medical procedures eCRF.

7.5.2. Prohibited and/or Restricted Treatments

During the course of the study, participants may not receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. Additionally, no other therapeutic monoclonal antibodies and no immunosuppressive medication may be administered while on this study.

While systemic corticosteroid therapy may interfere with the mechanism of action of STAR0602 and participants will be excluded if they are taking >10 mg per day of prednisone (or equivalent), the use of systemic corticosteroid is recommended in some settings: (1) infusion reactions (Table 20); (2) potential irAE management (Section 7.3.4); and (3) potential CRS (Table 28). Note that participants with a pre-existing history of adrenal insufficiency are excluded from study participation, if not well controlled (see Section 6.3).

Blood transfusions may not be given during the screening period (Day -21 to Day 0) for the sole purpose of meeting the hemoglobin eligibility criterion for study entry.

For Phase 2 Cohort 8 (primary primary stage 4 or recurrent NSCLC) STAR0602 + docetaxel combination as second-line therapy:

- Avoid concomitant use of docetaxel and drugs that inhibit CYP3A4 such as ketoconazole and protease inhibitors, particularly ritonavir since they may increase exposure to docetaxel. If systemic administration of a potent CYP3A4 inhibitor cannot be avoided, consider docetaxel dose reduction per USPI[36], PM[37], SmPC[38].

For Phase 2 Cohort 10 (mCRC MSS without TMB requirement) STAR0602 + CAMPTOSAR (irinotecan) combination as second-line therapy:

- Do not administer strong CYP3A4 inducers such as phenytoin, phenobarbital, carbamazepine, or St. John's wort with irinotecan. Consider substituting non-enzyme inducing therapies at least 2 weeks prior to initiation of CAMPTOSAR therapy. Do not administer strong CYP3A4 inducers with CAMPTOSAR unless there are no therapeutic alternatives.
- Do not administer irinotecan with strong CYP3A4 inhibitors such as ketoconazole, or other CYP3A4 inihbitors (e.g., clarithromycin, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telaprevir, voriconazole) or inhibitors of UGT1A1 (e.g., atazanavir, gemfibrozil, indinavir) per USPI, PM or SmPC. Discontinue strong CYP3A4 inhibitors at least 1 week prior to starting CAMPTOSAR therapy. Do not administer strong

[36] https://products.sanofi.us/taxotere/taxotere.pdf
[37] https://pdf.hres.ca/dpd_pm/00041993.PDF
[38] https://www.medicines.org.uk/emc/product/7206/smpc#gref

CYP3A4 or UGT1A1 inhibitors with CAMPTOSAR unless there are no therapeutic alternatives.

7.6. Restrictions

There are no restrictions regarding fluid or food intake, imaging, or subject activity.

7.7. Treatment Compliance

Site personnel will administer STAR0602 while the study subject is at the site. Administration information will be recorded on the eCRF.

7.8. Packaging and Labeling

[redacted]

7.9. Investigational Product Storage and Accountability

[redacted]

[redacted]

7.10. Investigational Product Retention at Study Site

[redacted]

[redacted]

8. STUDY PROCEDURES

This trial will be conducted in accordance with this protocol, Good Clinical Practice (GCP), the ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Council for Harmonisation (ICH)/GCP guidelines, and all applicable regulatory requirements.

The study procedures to be conducted for each participant are presented in tabular form in Section 2 and described in detail in sub-sections below. The study procedures will be performed at the time points indicated in Section 2 and as clinically indicated.

The Investigator must document any deviation from these protocol procedures in subject source data.

8.1. Informed Consent

Participants considered to qualify for study participation and who voluntarily agree to participate in the study (or legally acceptable representative agrees) will be required to sign an informed consent form (ICF) prior to any study procedures being performed. Imaging studies (e.g., CT, MRI, ultrasonography) to assess the tumor status as part of standard of care may be performed prior to participants signing ICF.

At the time of radiographic disease progression, participants who are otherwise gaining benefit from the study drug may be considered for continuation of treatment with STAR0602 at the discretion of the investigator (See Section 7.3.7). If decided, these participants will be re-consented to continue participating in the study. The written informed consent document provided to participants will detail all available therapies with potential clinical benefit that the subject may be foregoing to continue receiving the investigational product.

8.2. Study Identification Card

Participants will be provided with a study identification card for this study upon signature of the ICF, that may help health care providers who are not involved with the participant's cancer treatment, to identify that the subject has received a novel immunotherapy as well as to recognize rare or subtle symptoms of immune-oncology toxicity. The study identification card will also include an emergency contact number.

8.3. Baseline Demographics and Medical History

Subject demographic data will be collected at Screening and will include: age, sex, race, and ethnicity (if allowed per country-specific regulations).

A complete medical history will be obtained at Screening, including history of disease process other than the cancer under study (active or resolved) and concurrent illness, as well as any current medical treatments and / or significant surgeries for any condition. Information on all interventions (i.e., local and systemic therapy, surgery, and radiation treatment) related to the participant's cancer since the cancer diagnosis will also be collected.

8.4. Physical Examination

A full physical examination will be performed at the time points indicated in Section 2 and Appendices 7-12.

A complete physical examination will include general appearance, eyes, ears, nose, mouth, throat, neck, respiratory, cardiovascular, gastrointestinal/abdomen, lymphatic, musculoskeletal, skin, and neurologic exams. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic examinations will be performed.

Height in centimeters (cm) will be measured at Screening only.

A targeted physical examination may be performed at any time if required, at the discretion of the Investigator, and will include any organ system associated with an AE or a laboratory abnormality.

8.5. CT and/or MRI

An MRI/CT scan for disease status, as per RECIST v1.1 criteria, will be performed at the time points indicated in Section 2 and Appendices 7-12.

If PR or CR occurs, a confirmatory MRI/CT will be done after 4 weeks (no later than 5 weeks), with the same method used for the initial assessment as required by RECIST criteria, as an unscheduled visit.

Refer to Appendix 1 (A1.2) for CT/MRI methods of measurements as per RECIST v1.1. The imaging data will be transferred to a vendor for central storage and blinded, independent, central review at the sponsor's discretion.

8.6. Safety Assessments

Safety assessments are based on the evaluation of treatment-emergent AEs that occur from the time of initiation of administration of study drug through the EoT Visit or 28 days after the last dose of study drug (whichever is later) and determined based on signs, symptoms, physical examination findings and/or laboratory test results from enrolled participants as appropriate.

8.6.1. Adverse Events Assessments

8.6.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study IP. This includes events related to the study procedures.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study IP administration even though it may have been present before the start of the study.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments, which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being treated or expected progression, signs, or symptoms of the disease/disorder being treated, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is an AE.
- Situations in which an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Interventions for pre-dose conditions or medical procedures that were planned prior to study enrollment are not considered to be AEs. Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) themselves are not AEs; they are therapeutic measures for conditions that require the procedure or surgery. The condition for which the surgery is required is an AE if it occurs or is detected after the administration of the IP and is not the condition under study.

Disease progression (unless considered to be drug related by the Investigator) is not considered an AE or SAE and should not be reported as such. When there are reasonable grounds for suspicion that the event is caused by the study drug (i.e., there are facts or arguments to suggest a causal relationship), it must be considered as an adverse drug reaction (ADR). Unexpected ADR: An ADR that is not consistent with applicable product information or summary characteristics of the study drug.

Any stable or intermittent chronic condition that is present at the time that the subject is screened will be considered as baseline medical condition and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

8.6.1.2. Definition of Serious Adverse Events

An SAE is an AE that fulfils one or more of the following criteria:

- Results in death
- Is life- threatening (subject is at immediate risk of death from the event as it occurred)[1]

- Requires in subject hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization [2]
- Results in persistent or significant disability/incapacity [3]
- Results in a congenital anomaly/birth defect
- Is an important medical event [4]

[1] "Life threatening" means that the subject was at immediate risk of death at the time of the SAE; it does not refer to an SAE that hypothetically might have caused death if it were more severe.

[2] This means that hospital inpatient admission or prolongation of hospital stay was required for the treatment of the AE, or that one or the other occurred as a consequence of the event. Planned hospitalizations for elective surgery or other medical procedures that are not related to a treatment-emergent AE are not considered SAEs. The following events would not be considered hospitalizations for SAE reporting purposes: 24-hour hold for observation, admission to a hospice facility or nursing home, respite care, outpatient surgery, social admission (e.g., a homeless subject) or admission not associated with a precipitating clinical AE (e.g., elective or pre-planned surgery, or inpatient administration of subsequent chemotherapy, etc.).

[3] "Persistent or significant disability or incapacity" means a permanent or significant and substantial disruption of a person's ability to carry out normal life functions.

[4] Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Death due to PD of malignancy should not be reported as an SAE, if documented by use of appropriate method (e.g., as per RECIST v1.1). Any AE that occurred as a result of the PD should be reported in the appropriate manner.

8.6.1.3. Definition of Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as those AEs with onset after the first dose of study drug or existing events that worsen after the first dose during the study.

8.6.1.4. Clinical Laboratory Adverse Events

The following laboratory test abnormalities should be captured:

- Any laboratory test result, including those that worsen from baseline, that is considered clinically significant in the scientific judgement of the Investigator or meets the definition of an SAE;

- Any laboratory test result abnormality that requires discontinuation or interruption of any of the study drugs;
- Any laboratory test result abnormality that requires the subject to receive corrective therapy or treatment.

Any abnormal laboratory test result (e.g., hematology, biochemistry or urinalysis) or other safety assessment (e.g., vital signs, physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the Investigator and not related to underlying disease, is to be reported as an (S)AE.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

8.6.1.5. Dose-limiting Toxicities





8.6.1.6. Pregnancy

Any pregnancy in a female subject (or partner of a male subject) in which the estimated date of conception is either before the last visit or within 30 days of last study drug, or any exposure to study drug through breastfeeding during study treatment or within 60 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study drug.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see AE and SAE Reporting [Section 8.6.1.12.1]).

All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the Investigator becomes aware of the outcome.

A subject who becomes pregnant should be immediately withdrawn from the study. However, a subject who becomes pregnant may remain in the study if the Investigator judges that the potential benefit to the subject outweighs any potential risk to the subject or the fetus and the subject gives informed consent for the further participation.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

Details of all pregnancies in female partners of male participants will be collected after study drug administration and until 30 days following study drug administration. In order for the Sponsor or designee to collect any pregnancy surveillance information from the female partner of a male subject, the female partner must sign an ICF for disclosure of this information. The expected date of delivery or expected date of the end of the pregnancy, last menstruation, estimated conception date, pregnancy result and neonatal data, etc., should be included in the pregnancy surveillance information.

8.6.1.7. Adverse Event Severity and Relationship

Every effort must be made by the Investigator to categorize each AE according to its severity and its relationship to the study drug.

8.6.1.7.1. Severity

The assessment of severity of an AE will be rated according to the CTCAE v5.0 criteria with high level definition summarized in Table 21.

Table 21 Definitions of Adverse Event Severity

Grade 1 (Mild)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. The AE does not interfere with routine activities. The subject may experience slight discomfort.
Grade 2 (Moderate)	Moderate; minimal, local or noninvasive intervention indicated; The AE interferes with routine activities. The subject may experience significant discomfort.
Grade 3 (Severe)	Severe or medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated. The subject is unable to perform routine activities. The subject may experience intolerable discomfort or pain.
Grade 4 (Life Threatening)	Life-threatening consequences; urgent intervention indicated.
Grade 5 (Fatal)	Death related to AE

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events.
Based on the CTCAE v 5.0.

The term “severe” is used to describe the intensity of an AE; the event itself could be of relatively minor clinical significance (e.g., ‘severe’ headache). This is not the same as “serious.” Seriousness of AEs is based on the outcome of an AE and usually associated with events that pose a threat to a participant’s life or functioning.

8.6.1.7.2. Assessment of Relationship to STAR0602

Relationship of the AE attributed to STAR0602 will be documented.

Items to be considered when assessing the relationship of an AE to the study drug are:

- Temporal relationship of the onset of the event to the initiation of the study drug;
- The course of the event, especially the effect of discontinuation of study drug or reintroduction of study treatment, as applicable;
- Whether the event is known to be associated with the study drug or with other similar treatments;
- The presence of risk factors in the study subject known to increase the occurrence of the event;
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event.

Classification of Causality

The relationship of each AE to the study drug will be recorded on the CRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

Pregnancy or breastfeeding are exclusion criteria for this study. Pregnancy is not considered an AE unless there is cause to believe that the investigational drug may have interfered with the effectiveness of a contraceptive medication.

For Cohort 8 (primary stage 4 or recurrent NSCLC), relationship of the AE to docetaxel will be assessed per docetaxel USPI[45], PM[46], or SmPC[47].

For Cohort 10 (mCRC with pMMR/MSS), relationship of the AE to irinotecan will be assessed per irinotecan USPI[48], PM[49] or SmPC[50] .

8.6.1.8. Expectedness

STAR0602 can cause [redacted]

[redacted]

[redacted]

8.6.1.9. Clinical Significance

Clinical significance is primarily assessed by the local Investigator, following good clinical judgement and toxicity assessment guidelines in current clinical use. AE summaries will be reviewed by the SRC for all dose levels on regular basis.

8.6.1.10. Method for Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation. Care should be taken not to introduce bias when collecting AEs or SAEs. All AEs must be assessed by the Investigator to determine if the AE is potentially immune-mediated. Additional information will be collected on case report forms (CRFs) for any event which is potentially immune-mediated.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the subject to discontinue the study intervention or study.

8.6.1.11. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts.

All non-serious AEs will be followed to resolution, until stabilized, or if judged as no longer clinically significant, and reported to the Sponsor as requested, to the IRBs/IECs according to IRB/IEC policies (to include annual Continuing Review Reports), to the data safety monitoring board as required, and to the United States (US) FDA as required for the annual report. Nonserious AEs should be reported as SAEs if they become serious.

All SAEs will be followed to resolution until resolution, until the condition stabilizes, until the event is otherwise explained, or until the participant is lost to follow-up.

8.6.1.12. Reporting

8.6.1.12.1. AE and SAE Reporting

All AEs will be collected from the start of the first dose infusion until the EoT Visit or 28 days after the last dose of study drug (whichever is later) or until the subject initiates new anticancer therapy. All AEs, whether or not they are related to the study, must be recorded on the forms provided by the Sponsor.

AEs reported between the time the subject signed the informed consent and the administration of the first dose of study drug will be captured as medical history if not protocol-related.

Any AE made known to the Investigator must be reported by the Investigator to the Sponsor if it occurs during the clinical study, whether or not the AE is considered to be related to the IP. The Investigator is responsible for ensuring that all AEs that are observed by study site personnel or reported by a subject are recorded on the eCRF during the study and/or as described below.

Serious adverse events related to study drug must be reported within 24 hours to the Sponsor, including after the participant's final visit. All SAEs should be reported immediately (within 24 hours) to the Sponsor using the SAE reporting form, whether considered drug related or not, except for those SAEs identified as not needing immediate reporting (see Section 8.6.1.2 and Section 8.6.1.7) and must include an assessment of whether there is a reasonable possibility that the drug caused the event. The immediate reports should be followed promptly by detailed, written reports (within 1 business day of their receipt) including copies of hospital case reports, autopsy reports, and other documents requested by the Sponsor. The immediate and follow-up reports should identify participants by unique code numbers assigned to the trial participants rather than by the participants' names, personal identification numbers, and/or addresses. If the follow-up information changes the Investigator's assessment of causality, this should also be noted on the follow-up SAE form. Study endpoints that are SAEs (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the drug and the event. In that case, the Investigator must immediately report the event to the Sponsor.

The Investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the Sponsor or third-party vendor acting on behalf of the Sponsor to be filed in the Sponsor's Trial Master File. The Investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious ADRs to the regulatory authority(ies) and the IRB/IEC.

Serious adverse events, regardless of causality assessment, must be collected through the last visit and for 30 days after the participant's last dose or start day of another anticancer therapy, whichever is earlier. If the subject initiates new anticancer therapy within 30 days of STAR0602 initiation, then SAEs will be collected for 30 days following the last dose of STAR0602. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the Investigator to be related to the study drug or any protocol-required procedure should be reported to the Sponsor regardless of the length of time that has passed since study completion.

The Investigator must record nonserious AEs and report them to the Sponsor according to the timetable for reporting specified in the protocol.

Reporting of laboratory/vital sign abnormalities as both laboratory findings and AEs should be avoided. They should not be reported as AEs unless any one of the following are met:

- Any criterion for an SAE is fulfilled;
- A laboratory/vital sign abnormality causes the subject to discontinue from the study drug;

- A laboratory/vital sign abnormality causes the subject to interrupt the study drug;
- A laboratory/vital sign abnormality requires intervention, including study drug dose interruption or modification.

The AE term should be reported in standard medical terminology when possible: diagnosis or syndrome(s) if known, but signs or symptoms can be accepted if underlying cause is not known. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, severity and serious outcome (if applicable), and whether or not it caused the subject to discontinue the study. The Investigator may be asked to provide follow-up information, discharge summaries, and extracts from medical records or eCRFs.

A copy of these forms must be forwarded within 24 hours of awareness to attention of the Sponsor and Medical Monitor. Contact details will be provided in the project update report.

The Investigator should not wait to receive additional information to document fully the event before notification of an SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

Instances of death, congenital abnormality, or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the Investigator at any time after cessation of study drug administration and linked by the Investigator to this study, should be reported to the Medical Monitor.

Progression of disease by itself is not considered an AE but rather an expected outcome and a study endpoint and should not be reported as AEs or SAEs. Adverse events associated with PD and associated hospitalizations to treat the AE or SAE are reportable events.

Due to the coronavirus SARS-CoV-2 causing the coronavirus disease 2019 (COVID-19) pandemic, Investigators must ensure compliance with local governing legislation and reporting requirements associated with COVID-19 infections.

8.6.1.12.2. Regulatory Reporting Requirements for SAEs

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAE) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements. Safety reports will be reported to Regulatory Agencies per appropriate regulations (e.g., US FDA 21 Code of Federal Regulations 312.32) and to all participating investigators of this study.

8.6.1.12.3. Special Reporting Situations

Safety events of interest that may require expedited reporting or safety evaluation include, but are not limited to:

- Overdose of the IP is known or suspected. Adverse events associated with an overdose must be collected on the AE page of the eCRF for all overdosed participants, but the overdose itself is not considered an AE;
- Drug-drug interaction associated with the IP is suspected;
- Accidental or occupational exposure (e.g., inadvertent exposure to the IP of personnel at the study institution while preparing it for administration to the subject) to the IP is known or suspected;
- Medication error (defined as an unintended failure in the treatment process that leads to, or has the potential to lead to, harm to the subject) or "off-label use" (i.e., use outside of the intended use as defined in the study) is known or suspected;
- Misuse (situations where the IP is/are intentionally and inappropriately used not in accordance with the intended use as defined in the study) or abuse (persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects) of the IP is known or suspected;
- Transmission of an infectious agent associated with the IP is suspected.

Progression of the underlying neoplasm resulting in hospitalization or death (e.g., subject hospitalized for or dies from PD only, without any other SAE) will be documented as an anti-tumor activity outcome and not as an SAE. If an SAE occurs in a subject and it is unclear whether the event is related to PD, the SAE should be reported.

Special reporting situations should be recorded in the eCRF. Any special reporting situation that meets the criteria of an SAE should be recorded on the Safety Report Form of the eCRF.

8.6.1.13. Urgent Safety Measures

An urgent safety measure (USM) is an intervention that is not defined by the study and can be put in place with immediate effect without needing to gain prior approval by the Sponsor, relevant competent authorities, IRB/IEC, where applicable, in order to protect participants from any immediate hazard to their health and/or safety. Either the Investigator or the Sponsor can initiate a USM. The cause of a USM can be safety-, product- or procedure-related.

8.6.1.13.1. Reporting Urgent Safety Measures

In the event of a potential USM, the Investigator must contact the Sponsor (within 24 hours of awareness). Full details of the potential USM are to be recorded in the participant's medical records. The Sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be a USM, the Sponsor will take appropriate action to ensure the safety and welfare of the participants. These actions may include but are not limited to a change in study procedures or STAR0602 treatment, halting further registration in the study, or stopping the study in its entirety. The Sponsor or Sponsor's designee will notify the relevant

competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

8.6.1.14. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, ECGs, X-rays, and other potential safety assessment required or not required by protocol should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

8.6.1.15. Supply of New Information Affecting the Conduct of the Study

When new information becomes available that is necessary for conducting the study properly, the Sponsor will inform all Investigators involved in the study as well as the appropriate regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The Investigator will also inform the participants, who will be required to re-consent in order to continue in the study.

8.6.2. Vital Signs

Vital signs include heart rate, respiratory rate, temperature, and blood pressure (systolic and diastolic). Vital signs will be evaluated at time points indicated in Section 2 and Appendices 7-12.

8.6.3. 12-Lead Electrocardiograms

A 12-lead ECG will be performed at the time points specified in Section 2 and Appendices 7-12 with conventional lead placement. The subject will remain supine for at least 3 minutes prior to the ECG. The ECG results will be read by the Investigator or designee and results documented.

8.6.4. ECOG Performance Status

ECOG performance status will be assessed at time points indicated in Section 2 and Appendices 7-12.

The ECOG performance (Oken et al, 1982) will documented as the following:

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

8.6.5. Laboratory Tests

Investigators must document their review of each laboratory safety report.

Blood and urine samples will be collected at the time points specified in Section 2 and Appendices 7-12.

8.6.5.1. Clinical Laboratory Assessments

Clinical laboratory assessments will include the laboratory parameters described in Table 22.

[redacted]

8.6.5.2. Pharmacokinetic (PK) and Immunogenicity Assessments

PK and ADA blood sampling should be obtained according to the Schedule of Events (Table 1, Table 2, and Table 3). Details are also described in the Laboratory Manual for the scheduling timepoints, handling, labelling, and shipping of the PK and ADA blood samples. Based on review of data, changes to the sampling schedule may occur. It is essential that the actual time and date of collection of each blood sample be recorded in the participant's eCRF. The volume of blood to be collected per sample should be approximately 5 mL.

Serum concentrations of STAR0602 will be measured using a validated immunoassay. One serum sample will be collected at each time point indicated for STAR0602 PK evaluation in the Laboratory Manual.

The generation and characterization of ADAs directed against STAR0602 will be assayed using a validated, bespoke bridging immunoassay with appropriate confirmation assays and validated cut-points. Assessment of the binding specificity of any detected ADAs may be further assessed using other bespoke assays (e.g., neutralizing antibody [Nab] assays). One serum sample will be collected at each time point indicated for ADA evaluation in the Laboratory Manual.

8.6.5.3. Biomarker Studies



[redacted]

8.6.5.4. Sample Collection, Storage, and Shipping

Detailed instructions for blood, serum, urine and biopsy collection, labeling, processing, storage, and shipping will be provided to the site in the procedure laboratory manual(s).

Data obtained will be used for research, to assist in developing safer and more effective treatments and will not be used to change the diagnosis of the subject or alter the therapy of the subject. Any sample or derivatives (DNA, RNA, and protein) may be stored for up to 15 years to assist in any research scientific questions related to STAR0602 or cancers, and for potential diagnostic development.

Archived tumor tissue samples and blood samples for pharmacodynamics, and other biomarker assessments will be collected from all consented study participants, except where prohibited by regional or local laws.

Samples may be used for biomarker discovery and/or validation to identify blood or tumor biomarkers that may be useful to predict treatment response (efficacy, pharmacodynamics), PK, and/or safety-related outcomes. Samples may also be used for potential diagnostic development.

In addition, biomarkers identified in other clinical studies may also be assessed in samples collected from participants enrolled in this study. The decision to perform exploratory biomarker analysis may be based on the clinical outcome of the study and/or the signals observed in other clinical studies.

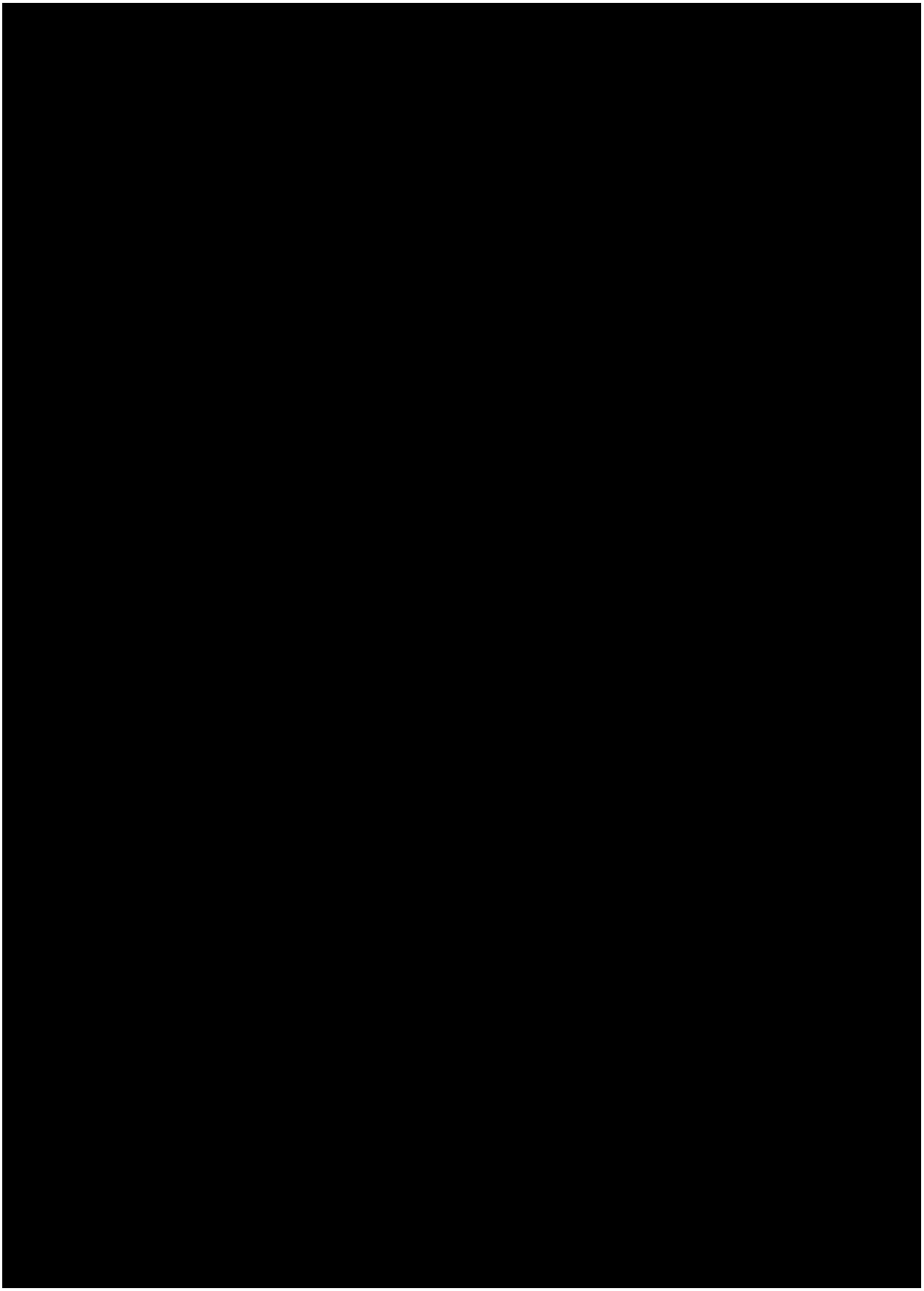
8.7. Efficacy Assessments

Tumor assessments will be obtained at Screening using CT and/or MRI scans plus any necessary tumor markers or other exams at time intervals as specified in Section 2. Disease status will be evaluated every 8 weeks (56 days) or every 9 weeks for [redacted] schedule or every 12 weeks for [redacted] schedule using CT and/or MRI plus tumor markers and other measures as appropriate for the sites of disease, accompanied by physical examination. For Cohorts 8 and 10, disease status will be evaluated every 6 weeks (42 ± 7 days) X 3, then every 9 weeks (63 ± 7 days) X 3, then every 12 weeks (84 ± 7 days).

For both Phase 1 and Phase 2, participants' tumor status will be evaluated every 8 weeks (56 days) per both iRECIST and RECIST v1.1 until EoT. For [redacted] tumor status will be evaluated every 9 weeks. For [redacted] tumor status will be evaluated every 12 weeks. For Cohorts 8 and 10, disease status will be evaluated every 6 weeks (42 ± 7 days) X 3, then every 9 weeks (63 ± 7 days) X 3, then every 12 weeks (84 ± 7 days).

All tumor assessment scans and photographs will be sent to an imaging core laboratory designated by the Sponsor for quality assessment, tumor lesions volumetric assessment, and archival for potential independent efficacy review.

Tumor assessments at Screening:



[redacted]

Tumor assessments during study:

[redacted]



8.8. Discontinuation Criteria

8.8.1. Discontinuation of Study or Study Drug

The Investigator may discontinue treating a subject with study drug or withdraw the subject from the study at any time for safety or administrative reasons. The subject may decide to discontinue study drug or withdraw from the study at any time for any reason. The reason for discontinuation will be documented.

For Phase 2 Cohort 8 or Cohort 10, participants who develop a clinically significant treatment-related AE that can be attributed to a specific agent among the combination therapy may choose to discontinue that particular therapy while continuing other therapies only after the Investigator feels it is clinically appropriate and after discussion with the Sponsor.

If a participant discontinues study intervention, the participant will enter the Follow-Up Period and complete protocol-specified off-treatment visits, procedures, and survival follow-up unless the participant withdraws consent.

An Investigator may discontinue a subject from the study drug for these primary reasons:

- A protocol violation occurs;
- AE(s)/ SAE(s);
- Pregnancy;
- Occurrence of a drug-related DLT;
- Drug interruption for ≥ 42 days;
- Lost to follow-up;
- The Sponsor or Investigator terminates the study;
- Withdrawal of consent by subject or proxy;
- Other.

Participants who are confirmed to have disease progression during the study but otherwise are achieving clinically meaningful benefit may choose to continue the treatment at the discretion of the Investigator, if clinically stable defined as:

- Absence of symptoms and signs indicating clinically significant progression of disease;
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status;
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., symptomatic pleural effusion, spinal cord compression).

Participants will be required to reconsent to continue treatment.

8.8.2. Subject Withdrawal

If a subject is withdrawn from the study or from STAR0602 dosing for any reason other than disease progression, the Sponsor must be alerted within 24 hours.

If a subject withdraws consent:

- The investigator will explain to the subject involved that the study will be discontinued, no additional study drug will be given to the subject and will provide appropriate medical treatment and other necessary measures for the subject.
- At the time of withdrawal or discontinuing from the study, if possible, an End of Treatment (EoT) visit should be conducted, as shown in Section 2.
- If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document such a destruction in the site study records.

8.8.3. Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible, counsel the subject on the importance of maintaining the assigned visit schedule, and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the subject continue to be unreachable, he/she will be considered to be lost to follow-up.
- If it is determined that a subject has died, the site will use permissible local methods to obtain the date and cause of death.

8.8.4. Study Site Discontinuation

The Sponsor reserves the right to close the study site at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

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

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

8.8.5. Study Enrollment Stopping Rules

Enrollment may be temporarily stopped if any of the following occurs:

- Any toxicity that is unexpected, significant, and unacceptable (based on SRC review and discussion);
- Two Grade 4 adverse events (except laboratory abnormalities) that are at least possibly related to the study drug;
- Any death, other than death related to PD, that occurs within 30 days of study drug administration.

If any of the above stopping criteria are met, an SRC meeting will occur to review the information and to recommend how to proceed.

8.8.6. Premature Stopping of Study

The Sponsor reserves the right to terminate the study at any time for any reason at the sole discretion of the Sponsor. The study may be prematurely stopped due to any the following reasons:

- The discovery of an unexpected, significant, or unacceptable risk to the participants enrolled in the study, or to potential study participants;
- A decision on the part of the Sponsor to suspend or discontinue the development of the study drug;
- Any other reason as determined by the Sponsor or SRC.

The Sponsor will be responsible for all decisions pertaining to prematurely discontinuing the study.

8.9. Appropriateness of Measurements



9. QUALITY CONTROL AND ASSURANCE

The Sponsor is implementing and maintaining quality assurance (QA) and quality control (QC) systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the contract research organization (CRO) will be applied.

The Sponsor or Sponsor's designee may arrange to audit the study at any or all institutions and facilities. The audit may include on-site review of regulatory documents and source documents. Direct access to these documents will be required by the auditors.

To ensure compliance with ICH GCP E6(R2) and all applicable regulatory requirements, the Sponsor or its representatives may conduct a QA audit. See Section 9.1 for more details regarding the audit process.

9.1. Audits and Inspections

As per ICH GCP and the Sponsor's audit plans, representatives of the Sponsor or the CRO's Clinical Quality Assurance Department (or designees), a regulatory authority, an IEC, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP principles, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

10. PLANNED STATISTICAL METHODS

The statistical analysis will be coordinated by the responsible study biostatistician. A Statistical Analysis Plan (SAP) will be written to provide details of the endpoint derivations and analysis methods, along with mock tables, listings, and figures. Any changes to the analyses planned in the SAP will be explained in the clinical study report.

10.1. General Considerations

Summary statistics will consist of the frequencies of each category of discrete variables, and of means, standard deviations, medians, minimum, and maximum values of continuous variables. Safety and anti-tumor activity summaries will be provided by dose level and schedule, and/or by tumor type. Response rates may be calculated for specific disease subgroups, if appropriate.

10.1.1. Study Endpoints

10.1.1.1. Phase 1: Dose Escalation

The Phase 1 primary endpoints are as follows:

- DLTs
- Safety (including but not limited to): TEAEs, SAEs, deaths, clinical laboratory abnormalities per NCI-CTCAE, Version 5.0, and CRS per ASTCT criteria

The Phase 1 secondary endpoints are as follows:

- ORR according to iRECIST
- DOR defined as time from the date of first documented PR/CR until the first documentation of confirmed disease progression per both iRECIST and RECIST v1.1
- DCR defined as the proportion of participants achieving CR+PR+SD per both iRECIST and RECIST v1.1
- STAR0602 PK parameters following single- and repeated IV infusions as data permit (e.g., AUCs, C_{max}, T_{max}, CL, Vss, single-dose $t_{½}$, and repeat-dose C_{max} and C_{trough})
- ADA incidence and titers after single- and repeat-IV dosing of STAR0602

The Phase 1 exploratory endpoints are as follows:

- Cell counts and frequency of Vβ6/Vβ10 T cell subsets in PBMCs by flow cytometry
- Expression levels of Vβ6/Vβ10 in T cells and other germline Vβ TCR variants in PBMCs and TILs in tumor tissue biopsy samples by gene expression analysis (e.g., using Nanostring assays)
- Levels of serum cytokine sand other soluble factors (e.g., sCD25) by immunoassay following single- and repeat-dosing of STAR0602
- PFS defined as the time from the initial infusion of study drug until documented disease progression or death from any cause per both iRECIST and RECIST v1.1

- OS
- ORR, DOR, DCR, PFS per iRECIST and RECIST, and OS in subgroups of TMB-H, MSI-H/dMMR and virally associated cancers, with each subgroup of participants combined across all dose cohorts. Subgroup analysis will be performed at the Sponsor's discretion
- ctDNA levels in the peripheral blood.

10.1.1.2. Phase 2: Dose Expansion

The Phase 2 primary endpoints are as follows:

- ORR defined as the proportion of participants who have CR + PR per iRECIST

The Phase 2 secondary endpoints are as follows:

- ORR per RECIST v1.1
- DOR per both iRECIST and RECIST v1.1
- DCR per both iRECIST and RECIST v1.1
- PFS defined as the time from the initial infusion of study drug until documented disease progression or death from any cause per both iRECIST and RECIST v1.1
- OS
- STAR0602 population PK parameters in expansion cohorts at the RP2D (e.g., C_{max}, AUC, CL, Vd)
- Safety (including but not limited to): TEAEs, SAEs, deaths, clinical laboratory abnormalities per NCI CTCAE, Version 5.0, and CRS per ASTCT criteria
- ADA incidence and titers after single- and repeat-IV dosing of STAR0602

The Phase 2 exploratory endpoints are as follows:

- Subgroup analyses (e.g., pooled analyses for TMB-H or MSI-H or both regardless of tumor histologies across cohorts) for ORR defined as the proportion of participants who have CR + PR per iRECIST at the Sponsor's discretion
- Cell counts and frequency of Vβ6/Vβ10 T cell subsets by flow cytometry
- Qualitative and semi-quantitative measurement of Vβ6/Vβ10 T cells in tumor tissue by Multiplex IHC/IF
- Changes in gene expression profile of T cells isolated from PBMCs, and TILs from tumor tissue
- TCR sequencing (TCRseq) of RNA extracted from TILs of the tumor biopsy tissue samples
- TIL phenotyping by flow cytometry (will be undertaken at selected sites with experience)
- ctDNA levels in the peripheral blood

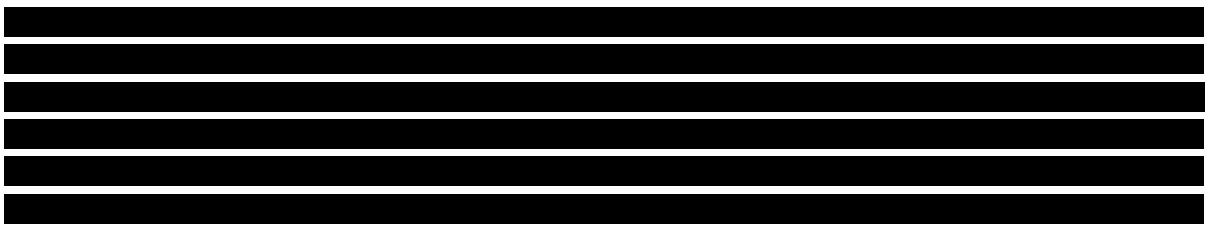
10.2. Determination of Sample Size

No formal statistical hypotheses are being tested in Phase 1. Analysis of the data obtained from Phase 1 will only utilize descriptive statistical methods. The total number of participants enrolled in Phase 1, Group A and Group B of the dose escalation phase, will depend on the frequency of DLTs and when the RP2D is determined. The maximum sample size is 48 and 36 participants for Group A and Group B, respectively. This estimated number of participants does not account for replacement of non-evaluable participants or the possibility of intermediate doses and adding backfill participants into any escalation cohort, up to 20, to allow for further evaluation of safety, PK, dosing schedule, and anti-tumor activity of STAR0602 at a given dose level below or at the MTD as part of the initial dose optimization plan.

In Phase 2 of the study, the dose expansion phase, the sample size for each cohort has been estimated using an optimal Simon's 2-stage design with the size of each cohort independently assessed except Cohorts 8 and 10. Assumptions for the null and alternate response rates are provided below.

Phase 2 will enroll from approximately 156 to 366 participants in 10 provisional cohorts. To assess futility within each cohort (except Cohorts 8 and 10), a Simon's 2-stage optimal design will be employed. For Cohort 1 (TMB-H) and Cohort 3 (CRC) , the null hypothesis (p0) that the true response rate is 0.05 will be tested against the one-sided alternative, pA > p0. In the first stage, 23 participants will be enrolled. If there are 1 or fewer responses (PR or CR) in these 23 participants, the study will be stopped. If there is more than 1 response, then 33 additional participants will be enrolled for a total of 56. In the extreme case that there are already more than 5 responses in the first stage, there is no need to have a second stage, and STAR0602 will be declared promising immediately after the first stage. The null hypothesis will be rejected if there are more than 5 responses. This design yields a one-sided type I error rate of 0.05 and power of 0.80 when the true response rate is 0.15.

For each of Cohort 2 and Cohorts 4 to 7 and 9, the null hypothesis (p0) that the true response rate is 0.05 will be tested against the one-sided alternative, pA > p0. In the first stage, 10 participants will be enrolled. If there are 0 responses in these 10 participants, enrollment to that cohort will be stopped. If there are 1 or more responses, then 19 additional participants will be enrolled for a total of 29 participants. In the extreme case that there are already more than 3 responses in the first stage, there is no need to have a second stage, and STAR0602 will be declared promising immediately after the first stage. The null hypothesis will be rejected if there are more than 3 responses. This design yields a one-sided type I error rate of 0.05 and power of 0.80 when the true response rate is 0.20.





10.3. Analysis Populations

Three general populations will be used for the purposes of this analysis for each treatment regimen as defined below:

- **Safety Population:** All participants who received at least one dose of the study drug. This population will be used for safety analyses.
- **Efficacy Population:** All participants with measurable disease on the baseline tumor assessment who received the planned treatment regimen and had at least 1 post-infusion radiographic tumor assessment. This population will be used for the analysis of efficacy endpoints.
- **Response Evaluable Population:** All participants in the Efficacy Population as well as participants who have died within 12 weeks of baseline and had no post-infusion radiographic tumor assessments. The Response Evaluable Population will be used for the primary efficacy ORR analysis.

- **Pharmacokinetic Population:** All participants who received at least one dose of the planned treatment regimen and had at least 1 post-infusion PK assessment. This population will be used for PK analyses.
- **Pharmacodynamic Population:** All participants who received at least one dose of the planned treatment regimen and had at least 1 post-infusion pharmacodynamic assessment. This population will be used for pharmacodynamic analyses.
- **Immunogenicity Population:** All participants who received at least one dose of the planned treatment regimen and had at least 1 post-infusion immunogenicity assessment. This population will be used for immunogenicity analyses.

10.4. Demographics and Baseline Characteristics

Demographic (age, sex race, ethnicity) and Baseline Characteristics (e.g., height, weight) will be summarized descriptively and presented by tumor type and overall.

10.5. Statistical Analysis of Efficacy Variables

ORR, DOR, DCR, and PFS will be determined per iRECIST. Sensitivity analyses will also be performed using RECIST v1.1 for the following variables.

- ORR will be calculated as the proportion of participants who have CR + PR. Exact two-sided 95% CIs will be constructed around the ORRs.
- DOR will be defined as time from the date of first documented PR/CR until the first documentation of confirmed disease progression.
- DCR will be calculated as the proportion of participants who remain free of disease progression (CR + PR + SD). Two sided exact 95% CIs will be constructed around the DCR.
- PFS will be calculated as the time from the initial infusion of study drug until documented disease progression or death from any cause. Participants with no PFS event (disease progression or death from any cause) will be censored at the date of their last tumor assessment. Any subject who dies after 2 or more missed assessments will also be censored at the date of their last tumor assessment. Kaplan-Meier estimates will be provided for the median PFS.
- OS will be calculated as the time from the initial infusion of study drug to death from any cause. Participants who do not die will be censored at the date that the subject was last known to be alive. Kaplan Meier estimates will be provided for the median OS.

10.6. Statistical Analysis of Pharmacokinetic Variables

Individual STAR0602 serum will be listed by time point and summarized by treatment group. Individual and mean STAR0602 serum time profiles for each treatment group will also be presented graphically. PK parameters will be listed and summarized using descriptive statistics, including arithmetic and geometric mean, median, standard deviation, coefficient of variation (CV), geometric CV, minimum, and maximum. Population PK analyses may be conducted using data from this study alone or combined with data from other studies.

Single- and multiple-dose PK parameters (C_{max}, T_{max}, AUC at terminal phase [AUC_{tau}], AUC from dosing to the time of the last measured concentration [AUC_{last}], AUC extrapolated to infinity [AUC_{inf}], C_{trough}, CL, Vss, and $t_{1/2}$) will be derived from STAR0602 serum concentration versus time data. Other PK parameters may also be reported, as applicable.

In addition, the exposure-response relationship between STAR0602 (dose, concentration, C_{max}, or AUC) and clinical activity (e.g., ORR) and safety will also be explored combining Phase 1 and Phase 2 data together if deemed appropriate.

In Phase 2 Dose Expansion, a population approach to the analysis of PK data will be undertaken. Serum STAR0602 concentration-time data together with data from Phase 1 Dose Escalation will be analyzed using a nonlinear, mixed effects model to determine both individual and population PK parameters and identify relevant covariates. PK sampling schedules for Phase 2 will be finalized based on PK data from Phase 1.

10.7. Immunogenicity Analysis

The proportion of participants who are negative for ADAs at baseline and become positive in this assay, the proportion of participants who are negative at baseline and remain negative, and those who have positive ADAs at baseline that increase or decrease in titer over the course of treatment will be summarized.

10.8. Pharmacodynamic Analysis

Pharmacodynamic assessments include measurements of sCD25; pSTAT5; changes in T cell markers (including expansion of Vβ6/Vβ10 T cells; Treg; memory cell compartments); measurements on tumor biopsies: TILs; Vβ6/Vβ10 T cells; immunoscore or similar.

PK, pharmacodynamic markers, immunogenicity summaries will be provided by initial dose cohort in Part 1 and by expansion cohort in Part 2. PK parameters will be evaluated and summarized for each dose cohort in Part 1 and in Part 2 and presented graphically. Pharmacodynamic markers: Changes from baseline in PD markers will also be evaluated and summarized for each dose cohort in Part 1 and for Part 2 and presented graphically. See Table 1, Table 2 and Table 3.

10.9. Safety Analysis

- General Safety: safety data, including vital signs, ECOG, ECGs, laboratory test results, and AEs, will be summarized by dose and assessment time points, as appropriate. Change from baseline will be included in summary tables for laboratory, ECG, and vital sign parameters. Shifts in grade from baseline to maximum post-baseline grade will be summarized for each dose level, as appropriate, for applicable laboratory data. Summaries of participants with AEs Grade ≥ 3 or laboratory values Grade ≥ 3 will be tabulated by dose level, as appropriate.
- Statistical Method for Phase 1 Dose Escalation and MTD determination

  In Group A of Phase 1, dose escalation will be based on 3 + 3 design and MTD is defined as the highest dose level at which < 33% of participants experience a DLT during the DLT Evaluation Period.

In Group B of Phase 1, the modified BOIN design will be employed for dose escalation with the target toxicity rate of 0.3 as described in Table 10. After Group B is completed, MTD will be determined based on isotonic regression as specified in Liu and Yuan (2015) in DLT evaluable population. Specifically, select as the MTD the dose for which the isotonic estimate of the toxicity rate is closest to the target toxicity rate of 0.3. If there are ties, select the higher dose level when the isotonic estimate is lower than the target toxicity rate and select the lower dose level when the isotonic estimate is greater than or equal to the target toxicity rate.

10.10. Interim Analysis

Interim monitoring using a snapshot of the database will be conducted to determine the MTD and/or RP2D, or to confirm safety and detect efficacy signals in participants with selected disease indications before the analysis for a clinical study report (CSR). Database locks are not required to perform these interim evaluations.

The data cutoff date for the CSR will be after 6 months of the last subject in and may be conducted before the last subject discontinues study drug in this study.

11. IRB OR IEC APPROVAL

The Investigator will ensure that this protocol, the site's ICF, any other written information provided to the participants, and any amendments to study documentation are reviewed and approved by an appropriate IRB/IEC.

The Investigator must obtain IRB/IEC approval for the study. Prior to subject enrollment, the Investigator or designee will provide the Sponsor with copies of the IRB/IEC approval of the Investigator, the study, and other study documentation provided to participants. If, during the study, it is necessary to amend study documentation, the IRB/IEC approval of an amended ICF must be obtained prior to new participants consenting to take part in the study using the amended form. The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. Copies of the IRB/IEC approval of the amended study documentation and approved materials will be provided to the Sponsor as soon as available.

All reviews and approval by IRB/IEC will be in accordance with GCP.

An Investigator who receives an Investigator safety report describing SAEs or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious ADRs from any other study conducted with the investigational product. The Sponsor or its representative will provide this information to the Investigator.

Progress reports and notifications of serious ADRs will be provided to the IRB/IEC according to local regulations and guidelines.

11.1. Ethical Conduct of the Study

This study will be conducted in compliance with the protocol, the ICH GCP, and all applicable regulations, including, where applicable, the Declaration of Helsinki. The study will also be carried out in keeping with applicable national and local laws and regulations. This may include an inspection by the Sponsor's representatives and/or regulatory representatives at any time.

In accordance with applicable local regulations, the Sponsor or designee will obtain approval from the appropriate regulatory agency prior to site initiating the study in that country or jurisdiction.

The Investigator will ensure that this protocol is reviewed and approved by the appropriate IRB/IEC. The IRB/IEC will also review and approve the site's ICF and any other written information provided to the subject. Prior to the enrollment of participants, the Investigator or designee will forward copies of the IRB/IEC approval and approved study documentation to the Sponsor for their records.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or local regulations;
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC and/or local regulations procedures;
- Providing oversight of the conduct of the study at the site and adherence to applicable local regulations.

11.2. Subject Information and Consent

The Investigator at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the study-related information provided. Participants must be informed that their participation is voluntary.

Participants will be required to provide consent that meets the requirements of local regulations and the IRB/IEC or study center. The participant's signed and dated informed consent must be obtained before conducting any study procedures. The participant's medical records must include a statement that informed consent was obtained prior to any study-related procedures and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF, where required per local regulations.

The Investigator(s) or the site assigned personnel must maintain the original, signed ICF. A copy of the signed ICF must be given to the subject.

The Investigator will obtain written informed consent from each subject participating in the study:

- Ensure that each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study and the exploratory biomarker assessments.
- Ensure that each subject is notified that they are free to withdraw from the study or the subsequent biomarker assessments at any time.
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided and discuss the study with their family or surrogates.
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure each original, signed ICF is stored in the Investigator's Study File/medical records.
- Ensure a copy of each signed ICF is given to the subject.

At the time of confirmed radiographic disease progression, participants who otherwise is achieving clinically meaningful benefit and who choose to continue receiving treatment with STAR0602 at the discretion of Investigator, will be required to reconsent. The written informed consent document provided to participants, will detail all available therapies with potential clinical benefit that the subject may be foregoing to continue receiving the investigational product.

11.2.1. Changes to the Protocol and Informed Consent Form

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative.

Any such changes which may affect a participant's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC and the concerned Competent Authorities. The exception to this is where modifications are necessary to eliminate an immediate hazard to study participants, or when the change involves only logistical or administrative aspects of the study (e.g., change in monitor, change in telephone number).

Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Investigator.

The Investigator or his/her representative will immediately inform the subject (as per local regulations, guidelines and procedures) whenever new information becomes available that may be relevant to the participant's consent or may influence the participant's willingness to continue participating in the study (e.g., report of serious ADR). The communication must be documented in the participant's medical records and whether the subject is willing to remain in the study or not must be confirmed and documented.

The Investigator or his/her representative must obtain informed consent from the subject on all updated ICFs throughout their participation in the study. The Investigator or his/her designee must reconsent participants with the updated ICF (when written consent required per local regulations) even if relevant information was provided verbally. The Investigator or his/her representative who obtained the informed consent and the subject should sign and date the ICF, when required per local regulations. A copy of the ICF will be given to the subject and the original will be placed in the participant's medical record. An entry should be made in the participant's records documenting the reconsent process.

11.3. Protocol Amendments

Any decision to amend the clinical trial application and/or associated documents (e.g., protocol, ICF, eCRF, Investigator's Brochure, etc.) will be made by the Sponsor.

The relevant regulations will be followed to determine what approvals from regulatory, IRB/IEC or local bodies are required. All required approvals will be obtained prior to implementation of the amendment, except as necessary to eliminate immediate safety hazards to participants in accordance with ICH E6 (R2), 4.5 and applicable regulatory requirements. The Sponsor will notify each participating Investigator site when the amendment can be implemented.

All changes to the consent form will be IRB/IEC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

11.4. Subject Confidentiality

Subject confidentiality and privacy are strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions as per local regulations. 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 research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/IEC, 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 participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each study 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 IRB/IEC, Institutional policies, or Sponsor requirements.

Subject research data, which are for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the designated CRO supporting the study. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the designated CRO's research staff will be secured, and password protected. At the end of the study, all study databases will be de-identified and archived by the designated CRO.

11.5. Safety Review Committee

All dose escalation decisions will be made by the SRC, which will consist of:

1. Site physicians
2. Company physicians
3. CRO physician, if applicable
4. Statistician
5. Independent (from Sponsor) pharmacovigilance safety expert(s)
6. Any other independent expert (e.g., PK or toxicologist) on an as-needed basis

All dose escalation decisions will be made by the SRC. Additionally, the SRC will continue safety monitoring in dose expansion phase with consistent safety data reviews and specified time points during enrollment.

11.6. Study Monitoring

Before an investigational study site can enter a subject into the study, a representative of the Sponsor will review the investigational study site to:

- Determine the adequacy of the facilities;
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor or its representatives and the Investigator.

During the study, a monitor from the Sponsor or its representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, data are being accurately recorded in the eCRFs, and that investigational product accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the CRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB/IEC.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

11.7. Case Report Forms and Study Records

Source documents must be maintained for each subject in the study, consisting of all demographic and medical information, including locally reported clinical laboratory data, etc. A copy of the signed ICF must be retained. All information on the eCRFs must be traceable to these source documents in the participant's file.

A validated electronic data capture (EDC) system will be used to enter subject data onto eCRFs. Data will be collected using the EDC system or paper CRFs and entered into a quality controlled clinical database. Prior to the start of the study, items to be included in the clinical database will be determined and suitable paper source documents, CRFs, and/or eCRFs will be created to ensure the appropriate collection of all required data. For participants who do not

qualify for the Treatment Period of the study, data collected during Screening Period will not be entered into the clinical database.

Clinical laboratory or PK data will be transmitted electronically from external vendors and reconciled against the clinical database.

The study file and all source data will be retained at the clinical site until notification is given by the Sponsor for destruction.

The Investigator (or designee) will not be given access to the EDC system until they have been trained. The Investigator must certify that the data entered into the eCRFs are complete and accurate. After database lock, the Investigator will receive an electronic copy of their subject data for archiving at the study site.

The eCRF will be programmed with edit checks to file at entry for data integrity checks. Alongside source data verification, manual queries will be raised within the EDC system based upon scientific, safety, medical coding and data integrity review. The Investigator (or designee) will correct any entries identified as being in error until the subject records are deemed complete and all queries closed. All eCRF changes are fully audited in accordance with ICH GCP.

Upon final database lock, all subject data pertaining to the study including EDC and external data (e.g., specialist laboratory data) will be returned to the Sponsor via secure electronic media.

11.8. Protocol Violations/Deviations

All protocol deviations are to be documented and reported on a timely manner to the Sponsor. A dedicated Protocol Violations/Deviation list will be defined and will be used as source document and periodically monitored. Compliance with the protocol, and any trends, will be assessed by the number and proportion of participants with protocol deviations, globally and at each site. Major deviations will be escalated and will require medical review by the Medical Monitor and/or Sponsor medical team and will include decision and rationale to justify the subject´s continuation or discontinuation from the study.

11.9. Source Documentation

Source data should be available at the site to document the existence of the participants and to substantiate the integrity of study data collected. Source data should include the original documents relating to the study, as well as the medical treatment and medical history of the subject. The Investigator should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study participants and supports the information entered in the applicable system. Source data should be attributable, legible, contemporaneous, original, accurate and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary. If source data are created (first entered), modified, maintained, archived, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such systems should be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, study-related assessments,

AE tracking, and/or drug accountability. Paper records from electronic systems used in place of electronic format should be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information, if applicable). All printed records should be kept in the subject file and be available for archiving.

The Investigator / institution should maintain the study documents as specified in Section 8 (Essential Documents for the Conduct of a Clinical Trial) of ICH GCP E6 (R2) and as required by the applicable regulatory requirement(s). The Investigator should take measures to prevent accidental or premature destruction of these documents.

Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the Investigator must make available for direct access all requested study-related records.

With the agreement of the subject, the Investigator may inform the participant's primary care physician of the participant's participation in the study and may forward any clinically significant findings from clinical tests. The primary care physician may contact the Investigator for any further information regarding the participant's participation in the study. The subject has the right to request access to and request corrections of his or her medical records.

11.10. Data Generation and Analysis

The data will be entered into a validated database. Guidance on the completion of the applicable system will be provided in a separate document.

Subject data relating to the study will be recorded in the applicable system. The Investigator is responsible for ensuring that data entries in the system are accurate and correct.

The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting regulatory guidelines for the handling and analysis of data for clinical trials.

The Investigator must permit study-related monitoring, audits, IRB/IEC review as applicable, and regulatory agency inspections as required and provide direct access to source data documents.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Records and documents, including signed ICFs (as applicable), pertaining to the conduct of this study must be retained by the Investigator according to applicable local regulatory requirements, after study completion. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

11.11. Retention of Data

The Investigator must maintain all documentation relating to the study for a minimum period of 30 years from the IP administration, as required by applicable regulations and guidelines, or institution procedures, or for the period specified by The Sponsor, whichever is longer. If it becomes necessary for the Sponsor or its representative, or the Regulatory Authority to review any documentation relating to the study, the Investigator must permit access to such records.

Study records should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention/at least 25 years after the end of the clinical trial. These documents should be retained for a longer period, however, if required by applicable local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

The medical files of participants shall be archived in accordance with applicable local regulations.

11.12. Data Protection

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited unless the subject provides written consent or approval. Additional medical information may be given only after approval of the subject to the Investigator or to other appropriate medical personnel responsible for the participant's well-being.

The Sponsor shall not disclose any confidential information on participants obtained during the performance of their duties in the study without justifiable reasons.

Even though any individuals involved in the study, including the study monitors and auditors, may get to know matters related to a participant's privacy due to direct access to source documents, or from other sources, they may not disclose the content to third parties.

The Sponsor affirms the participant's right to protection against invasion of privacy. Only a subject identification number will identify subject data retrieved by the Sponsor. However, the Sponsor requires the Investigator to permit the Sponsor, Sponsor's representative(s), the IRB/IEC and when necessary, representatives of the regulatory health authorities to review and/or to copy any medical records relevant to the study.

The Sponsor agrees to comply and process personal data in accordance with all applicable privacy laws and regulations, including, without limitation, the Personal Information Protection Law in Japan, if applicable, and privacy laws in the US. If the services will involve the collection or processing of personal data (as defined by applicable data protection legislation) within the European Economic Area (EEA), then the Sponsor shall serve as the controller of such data, as defined by the EU Data Protection Directive (DPD), and Investigator and/or third party shall act only under the instructions of the Sponsor in regard to personal data. If the Sponsor is not based in the EEA, the Sponsor must appoint a third party to act as its local

data protection representative or arrange for a co-controller established in the EU for data protection purposes in order to comply with the DPD.

11.13. Dissemination of Clinical Study Data

Study data will be reported as required by local regulations.

Information concerning the product, patent applications, processes, unpublished scientific data, and other pertinent information is confidential and remains the property of the Sponsor. Details should be disclosed only to the persons involved in the approval or conduct of the study. The Investigator may use this information for the purpose of the study only. It is understood by the Investigator that the Sponsor will use the information obtained during the study in connection with the development of the product and therefore may disclose it as required to other clinical investigators or to regulatory agencies. In order to allow for the use of the information derived from this study, the Investigator understands that he/she has an obligation to provide the Sponsor with all data obtained during the study.

11.14. Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 Code of Federal Regulations (CFR) §54. In addition, Investigators must commit to promptly updating this information if any relevant changes occur during the study and for a period of 1 year after the completion of the study.

11.15. Publication and Disclosure Policy

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996 and the General Data Protection Regulation (European Union) 2016/679.

Data are the property of the Sponsor and cannot be published without prior authorization from the Sponsor, but data and publication thereof will not be unduly withheld.

11.16. Financing and Insurance

The Sponsor has covered this study by means of an insurance of the study if required per national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator’s file.

Refer to the clinical trial site agreement for details.

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13. APPENDICES

Appendix 1: Response Evaluation Criteria in Solid Tumors Version 1.1

The following paragraphs represent a reference to the RECIST criteria (Version 1.1; Eisenhauer et al, 2009).

A 1.1 Measurability of Tumor at Baseline – Definitions

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as follows:

Measurable – the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions – tumor lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest X-ray, and as ≥ 10 mm with CT scan or clinical examination (using calipers). Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). Malignant lymph nodes must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters) by use of a ruler or calipers. Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Non-measurable lesions – all other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Nodes that have a short axis < 10 mm at baseline are considered non-pathological and should not be recorded or followed.

Target lesions – when more than one measurable tumor lesion or malignant lymph node is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

Note: Pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum.

At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be calculated and recorded.

Non-target lesions – all non-measurable lesions (or sites of disease) including pathological nodes (those with short axis ≥ 10 mm but < 15 mm), plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not

required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

A 1.2 Methods of Measurements

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

Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent. While on trial, all target lesions recorded at baseline should have their actual measurements recorded on the eCRF at each subsequent evaluation, even when very small (e.g., 2 mm). 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. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion.”

Clinical lesions – clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm 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 recommended. If feasible, digital imaging is preferred.

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 ≥ 20 mm 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). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

Ultrasound – ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the trial, confirmation by CT should be obtained.

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 studies where recurrence following CR or surgical resection is an endpoint.

Tumor markers – tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in CR.

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 when the measurable tumor has met criteria for response or SD is advised to differentiate between response or SD and PD.

A 1.3 Tumor Response Evaluation

All participants will have their BEST RESPONSE from the start of trial treatment until the EoT classified as outlined below. Refer to Table 25 and Table 26.

CR – disappearance of all target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10 mm (**Note:** continue to record the measurement even if < 10 mm and considered CR). Tumor markers must have normalized. Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted.

PR – at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non-target lesions must be non-PD.

SD – neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on trial.

PD – at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on trial (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute PD (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment, for example where the tumor burden appears to have increased by at least 73% in volume (which is the increase in volume when all dimensions of a single lesion increase by 20%). Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but on further documentation, the earlier date must be used.





A 1.4 Frequency of Tumor Re-Evaluation

Tumors should be assessed at the time points indicated in the Schedules of Events (Table 1, Table 2, and Table 3). Additional assessments may be performed according to local institutional guidelines.

A 1.5 Date of Progression

This is defined as the first day when the RECIST v1.1 criteria for PD are met.

A 1.6 Reporting of Tumor Response

All participants included in the trial must be assessed for response to treatment, even if there is a major protocol treatment deviation or if they are ineligible, or not followed/re-evaluated. Each subject will be assigned one of the following categories: CR, PR, SD, PD, early death from malignant disease, early death from toxicity, early death from other cause or unknown (not assessable, insufficient data).

‘Early death’ is defined as any death occurring before the first per protocol time point of tumor re-evaluation. The responsible Investigator will decide if the cause of death is malignant disease, toxicity, or other cause. Participants for whom response is not confirmed will be classified as "unknown," unless they meet the criteria for SD (or the criteria for PR in case of an unconfirmed CR). Participants’ response will also be classified as "unknown" if insufficient data were collected to allow evaluation per these criteria.

Appendix 2: iRECIST

Tumor progression in this clinical trial may be evaluated by the investigator using modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics (iRECIST) based on the 2017 article by Seymour et al., titled *iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics.*

These guidelines are an adaptation of RECIST v1.1. iRECIST is based on RECIST v1.1. Responses assigned using iRECIST have a prefix of "i"— e.g., "immune" complete response (iCR) or partial response (iPR), and unconfirmed progressive disease (iUPD) or confirmed progressive disease (iCPD) to differentiate them from responses assigned using RECIST v1.1. Similar nomenclature is used for stable disease (iSD). New lesions are assessed and subcategorized into those that qualify as target lesions (new lesion, target) or non-target lesions (new lesion, non-target). RECIST allows the site to select up to 5 target lesions at baseline, 2 per organ, if clinically relevant via CT/MRI scans or by electronic calipers for skin lesions.

Assessment and Decision at RECIST v1.1 Progression

For participants who are clinically stable but show evidence of radiological PD by RECIST v1.1 as determined by the investigator, the investigator will decide whether to allow a subject to continue to receive study treatment until repeat imaging is obtained (using iRECIST for subject management [see Table 27]). This decision by the investigator should be based on the participant's overall clinical condition.

Clinical stability is defined as the following:

[redacted]

Any subject deemed **clinically unstable** should be discontinued from study treatment at site-assessed first radiologic evidence of PD, and is not required to have repeat tumor imaging for confirmation of PD by iRECIST.

If the investigator decides to continue treatment, the subject may continue to receive study treatment and the tumor assessment should be repeated 4 to 8 weeks later to confirm PD by iRECIST, per Investigator assessment.

Tumor flare may manifest as any factor causing radiographic progression per RECIST v1.1, including:

- Increase in the sum of measurements of target lesion(s) identified at baseline to ≥ 20% and ≥ 5 mm from nadir
- Unequivocal progression of nontarget lesion(s) identified at baseline
- Development of new lesion(s)

iRECIST defines new response categories, including iUPD (unconfirmed progressive disease) and iCPD (confirmed progressive disease). For purposes of iRECIST assessment, the first visit

showing progression according to RECIST v1.1 will be assigned a visit (overall) response of iUPD, regardless of which factors caused the progression.

At this visit, target and nontarget lesions identified at baseline by RECIST v1.1 will be assessed as usual.

New lesions will be classified as measurable or nonmeasurable, using the same size thresholds and rules as for baseline lesion assessment in RECIST v1.1. From measurable new lesions, up to 5 lesions total (up to 2 per organ), may be selected as New Lesions – Target. The sum of measurements of these lesions will be calculated and kept distinct from the sum of measurements for target lesions at baseline. All other new lesions will be followed qualitatively as New Lesions – Non-target.

Assessment at the Confirmatory Imaging

On the confirmatory imaging, the subject will be classified as progression confirmed (with an overall response of iCPD), or as showing persistent unconfirmed progression (with an overall response of iUPD), or as showing disease stability or response (immune-based stable disease/immune-based partial response/immune-based complete response [iSD/iPR/iCR]).

Confirmation of Progression

Progression is considered confirmed, and the overall response will be iCPD, if ANY of the following occurs:

- Any of the factors that were the basis for the initial iUPD show worsening
  - For target lesions, worsening is a further increase in the sum of measurements of ≥ 5 mm, compared to any prior iUPD time point
  - For nontarget lesions, worsening is any significant growth in lesions overall, compared to a prior iUPD time point; this does not have to meet the "unequivocal" standard of RECIST v1.1
  - For new lesions, worsening is any of these:
    - An increase in the new lesion sum of measurements by ≥ 5 mm from a prior iUPD time point
    - Visible growth of new nontarget lesions
    - The appearance of additional new lesions
- Any new factor appears that would have triggered PD by RECIST v1.1

Persistent iUPD

Progression is considered not confirmed, and the overall response remains iUPD, if:

- None of the progression-confirming factors identified above occurs; AND
- The target lesion sum of measurements (initial target lesions) remains above the initial PD threshold (by RECIST v1.1).

Additional imaging for confirmation should be scheduled 4 to 8 weeks from the imaging on which iUPD is seen. This may correspond to the next visit in the original visit schedule. The

assessment of the subsequent confirmation imaging proceeds in an identical manner, with possible outcomes of iCPD, iUPD, and iSD/iPR/iCR.

Resolution of iUPD

Progression is considered not confirmed, and the overall response becomes iSD/iPR/iCR, if:

- None of the progression-confirming factors identified above occurs; AND
- The target lesion sum of measurements (initial target lesions) is not above the initial PD threshold.

The response is classified as iSD or iPR (depending on the sum of measurements of the target lesions), or iCR if all lesions resolve.

In this case, the initial iUPD is considered to be pseudo-progression, and the level of suspicion for progression is "reset." This means that the next visit that shows radiographic progression, whenever it occurs, is again classified as iUPD by iRECIST, and the confirmation process is repeated before a response of iCPD can be assigned.

Management Following the Confirmatory Imaging

If repeat imaging does not confirm PD per iRECIST, as assessed by the investigator, and the subject continues to be clinically stable, study treatment may continue and follow the regular imaging schedule. If PD is confirmed, participants will be discontinued from study treatment.

NOTE: If a subject has confirmed radiographic progression (iCPD) as defined above, but the subject is achieving a clinically meaningful benefit, an exception to continue study treatment may be considered following consultation with the Sponsor. In this case, if study treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in the protocol.

Detection of Progression at Visits After Pseudo-progression Resolves

After resolution of pseudo-progression (i.e., achievement of iSD/iPR/iCR), iUPD is indicated by any of the following events:

- Target lesions
  - Sum of measurements reaches the PD threshold (≥ 20% and ≥ 5 mm increase from nadir) either for the first time, or after resolution of previous pseudo-progression. The nadir is always the smallest sum of measurements seen during the entire trial, either before or after an instance of pseudo-progression.
- Non-target lesions
  - If nontarget lesions have never shown unequivocal progression, their doing so for the first-time results in iUPD.
  - If nontarget lesions have shown previous unequivocal progression, and this progression has not resolved, iUPD results from any significant further growth of nontarget lesions, taken as a whole.
- New lesions
  - New lesions appear for the first time

- Additional new lesions appear
- Previously identified new target lesions show an increase of ≥ 5 mm in the new lesion sum of measurements, from the nadir value of that sum
- Previously identified nontarget lesions show any significant growth

If any of the events above occur, the overall response for that visit is iUPD, and the iUPD evaluation process (see Assessment at the Confirmatory Imaging above) is repeated. Progression must be confirmed before iCPD can occur.

The decision process is identical to the iUPD confirmation process for the initial PD, with one exception: if new lesions occurred at a prior instance of iUPD, and at the confirmatory imaging the burden of new lesions has increased from its smallest value (for new target lesions, the sum of measurements is ≥ 5 mm increased from its nadir), then iUPD cannot resolve to iSD or iPR. It will remain iUPD until either a decrease in the new lesion burden allows resolution to iSD or iPR, or until a confirmatory factor causes iCPD.

Additional details are provided in the iRECIST publication (Seymour et al., 2017).

Table 27 iRECIST Clinical Management

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST v1.1	Repeat imaging at 4 to 8 weeks to confirm PD.	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging by site by iRECIST.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment
Repeat tumor imaging confirms PD (iCPD) by iRECIST per investigator assessment	No additional imaging required.	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional imaging required.	Not applicable
Repeat tumor imaging shows iUPD by iRECIST per investigator assessment	Repeat imaging at 4 to 8 weeks to confirm PD. May occur at next regularly scheduled imaging visit.	Continue study treatment at the investigator's discretion.	Repeat imaging at 4 to 8 weeks to confirm PD per investigator's discretion only.	Discontinue treatment

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Repeat tumor imaging shows iSD, iPR, or iCR by iRECIST per investigator assessment.	Continue regularly scheduled imaging assessments.	Continue study treatment at the investigator's discretion.	Continue regularly scheduled imaging assessments.	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule.

Abbreviations: iCPD = iRECIST-confirmed progressive disease, iCR = iRECIST complete response, iRECIST = modified Response Evaluation Criteria in Solid Tumors 1.1 for immune-based therapeutics, iSD = iRECIST stable disease, iUPD = iRECIST unconfirmed progressive disease, PD = progressive disease, RECIST v1.1 = Response Evaluation Criteria in Solid Tumors version 1.1.

Appendix 3: General Guidelines for Grading and Managing CRS

Table 28 General Guidelines for Grading and Managing Cytokine Release Syndrome

CRS Grade [a]	Symptom	Symptomatic treatment	Tocilizumab	Corticosteroids
Grade 1	Fever only	• Admit to hospital, or monitor,in appropriate clinical setting • Acetaminophen and hypothermia blanket as needed for fever • Ibuprofen if fever is not controlled with above; use with caution or avoid if thrombocytopenic • Assess for infection with blood and urine cultures, and chest x ray • Consider antibiotics and filgrastim (if neutropenic) • IV fluids as needed • Symptomatic management of constitutional symptoms and organ toxicities	If persistent (greater than 3 days) or refractory fever, consider managing as Grade 2.	Not applicable
Grade 2	Hypotension not requiring vasopressors	• IV fluid • Manage fever and constitutional symptoms as in Grade 1 CRS	If not responding to the treatment as shown in the column "Symptomatic treatment", manage CRS per current practice guidelines, or administer tocilizumab[b] 8 mg/kg intravenously over 1 hour (not to exceed 800 mg). • If no clinical improvement in the signs and symptoms of CRS after the first dose, repeat tocilizumab every 8 hours as needed. Limit to a maximum of	If not responding to the treatment as shown in the column "Symptomatic treatment", manage CRS per current practice guidelines, or administer dexamethasone 10 mg IV once daily. • If improving, manage as Grade 1 above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate.
	Hypoxia requiring low-flow nasal cannula or blow-by	• Use supplemental oxygen as needed • Manage fever and constitutional symptoms as in Grade 1 CRS		

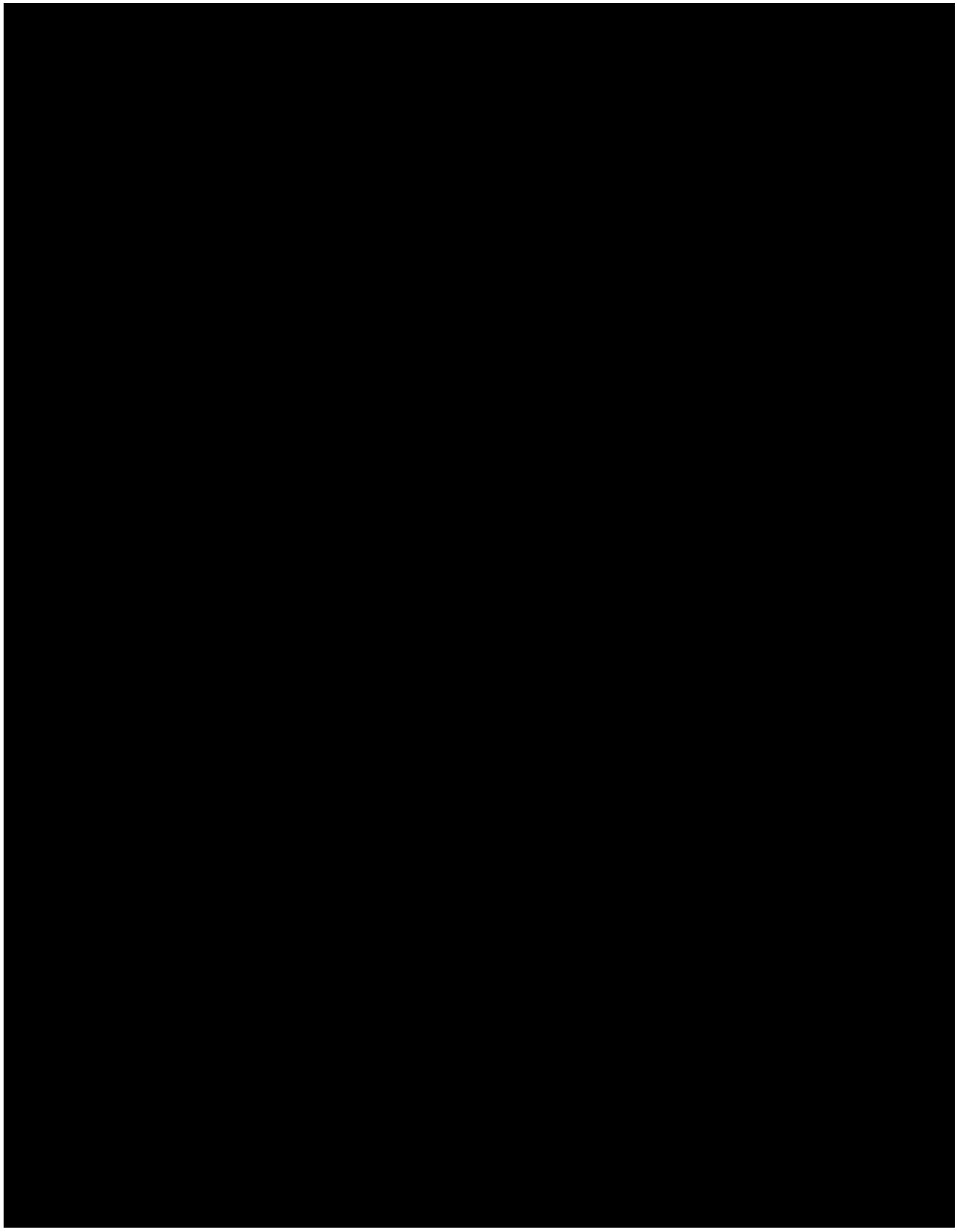
			3 doses in a 24- hour period; maximum total of 4 doses. • If improving, discontinue tocilizumab.	• If not improving, manage as appropriate grade below.
Grade 3	Hypotension requiring a vasopressor with or without vasopressin	Intravenous fluids, and a vasopressor with or without vasopressin	Per Grade 2. • If improving, manage as appropriate grade above. • If not improving, consider alternative therapy.	Dexamethasone 10 mg intravenously three times a day. • If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then quickly taper as clinically appropriate. • If not improving, manage as Grade 4.
	Hypoxia requiring high-flow nasal cannula, face mask, non-rebreather mask, or venturi mask	High-flow oxygen		
Grade 4	Hypotension requiring multiple vasopressors (excluding vasopressin)	Intravenous fluids and multiple vasopressor(s)	Per Grade 2. • If improving, manage as appropriate grade above. • If not improving, consider alternative therapy[c].	Administer methylprednisolone 1000 mg intravenously once per day for 3 days. • If improving, manage as appropriate grade above and continue corticosteroids until the severity is Grade 1 or less, then taper as clinically appropriate. • If not improving, consider methylprednisolone 1000 mg 2 to 3 times a day or alternate therapy[c].
	Hypoxia requiring positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	Positive pressure ventilation (e.g., CPAP, BiPAP, intubation and mechanical ventilation)		

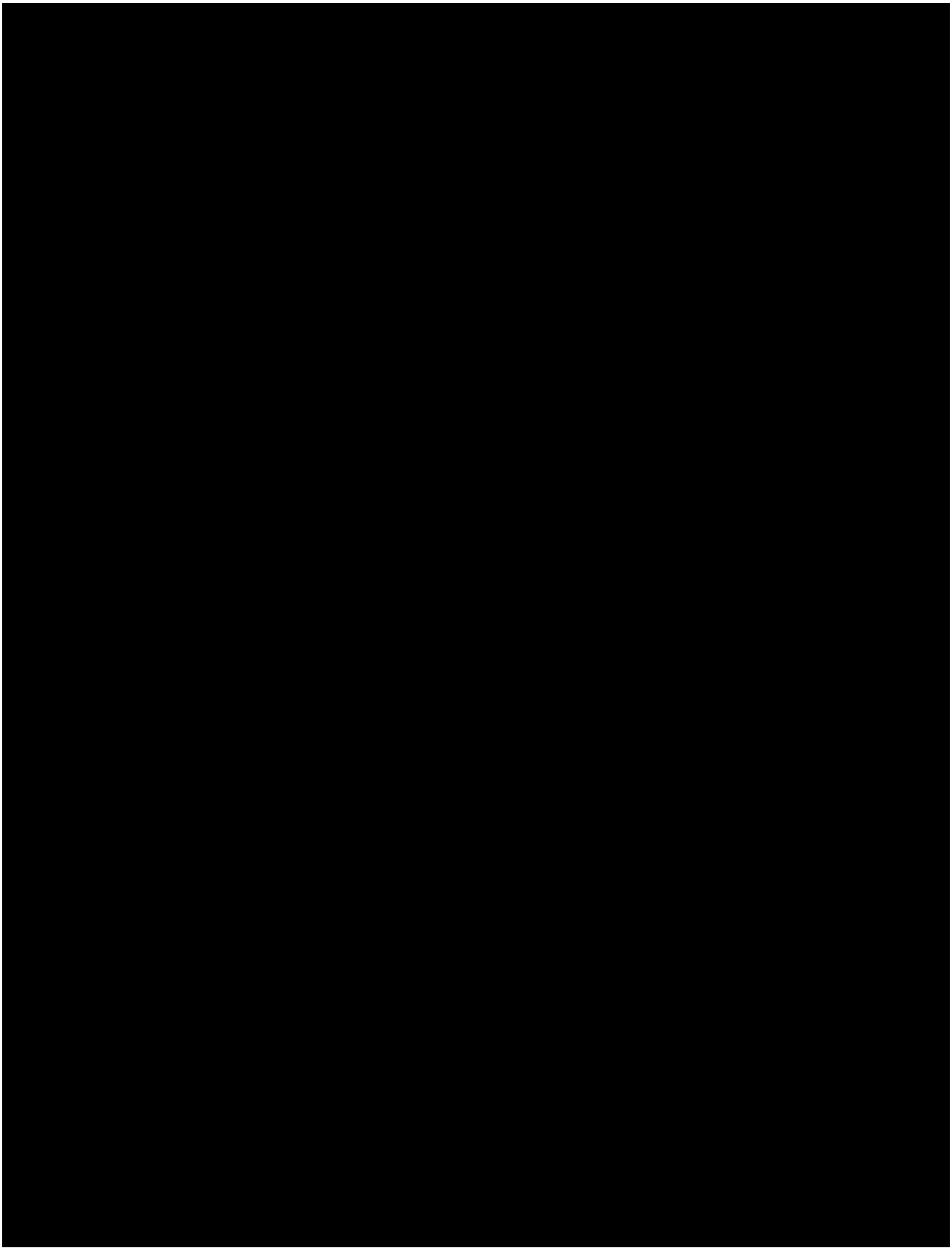
Abbreviations: ASTCT = American Society for Transplantation and Cellular Therapy; ATG = antithymocyte globulin; CRS = cytokine release syndrome; IVIG = intravenous immunoglobulin G

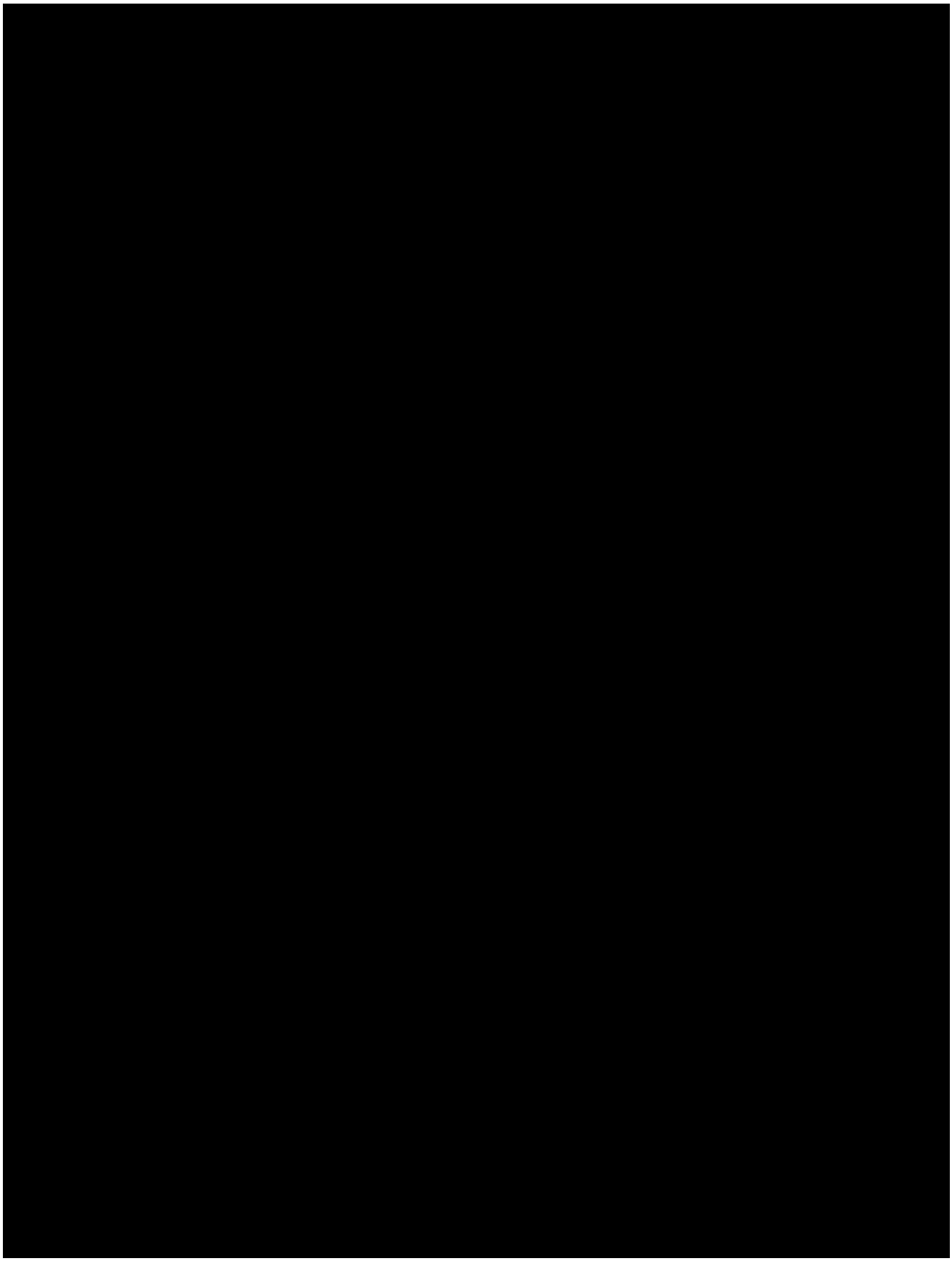
1. Grading per ASTCT CRS consensus criteria
2. Refer to tocilizumab Prescribing Information for details
3. Alternative therapy includes anti-cytokine and anti-T cell therapies as per institutional policy and published guidelines such as (but not limited to) anakinra, siltuximab, ruxolitinib, cyclophosphamide, IVIG and ATG

Sources: Adapted from Lee et al., 2018; Maus et al, 2020; Neelapu et al., 2018; prescribing information for YESCARTA, KYMRIAH, BLINCYTO, KIMMTRACK, LUNSUMIO, TECVAYLI, EPKINLY, and COLUMVI

Appendix 4: STAR0602 PK/Pharmacodynamic Modelling

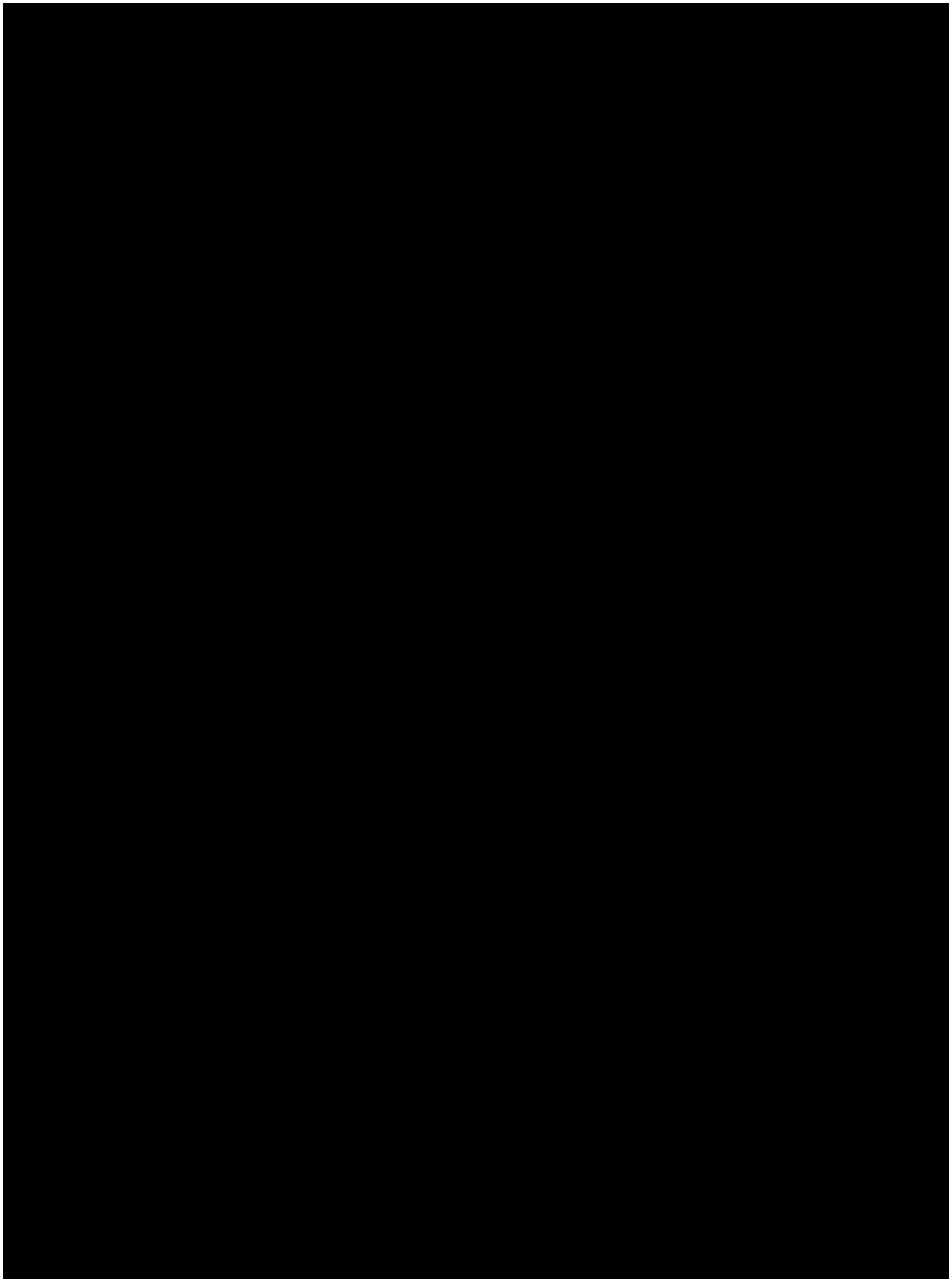


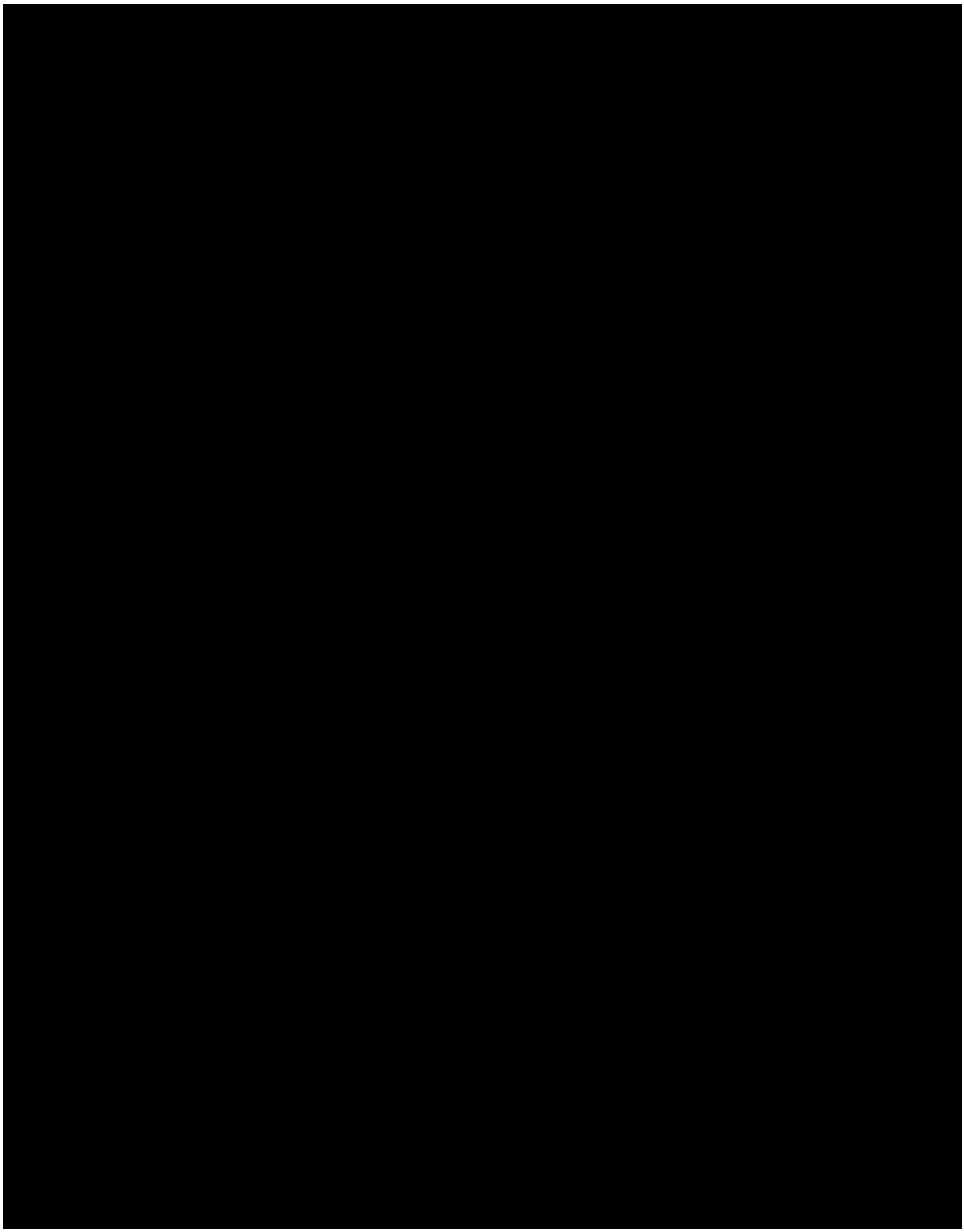




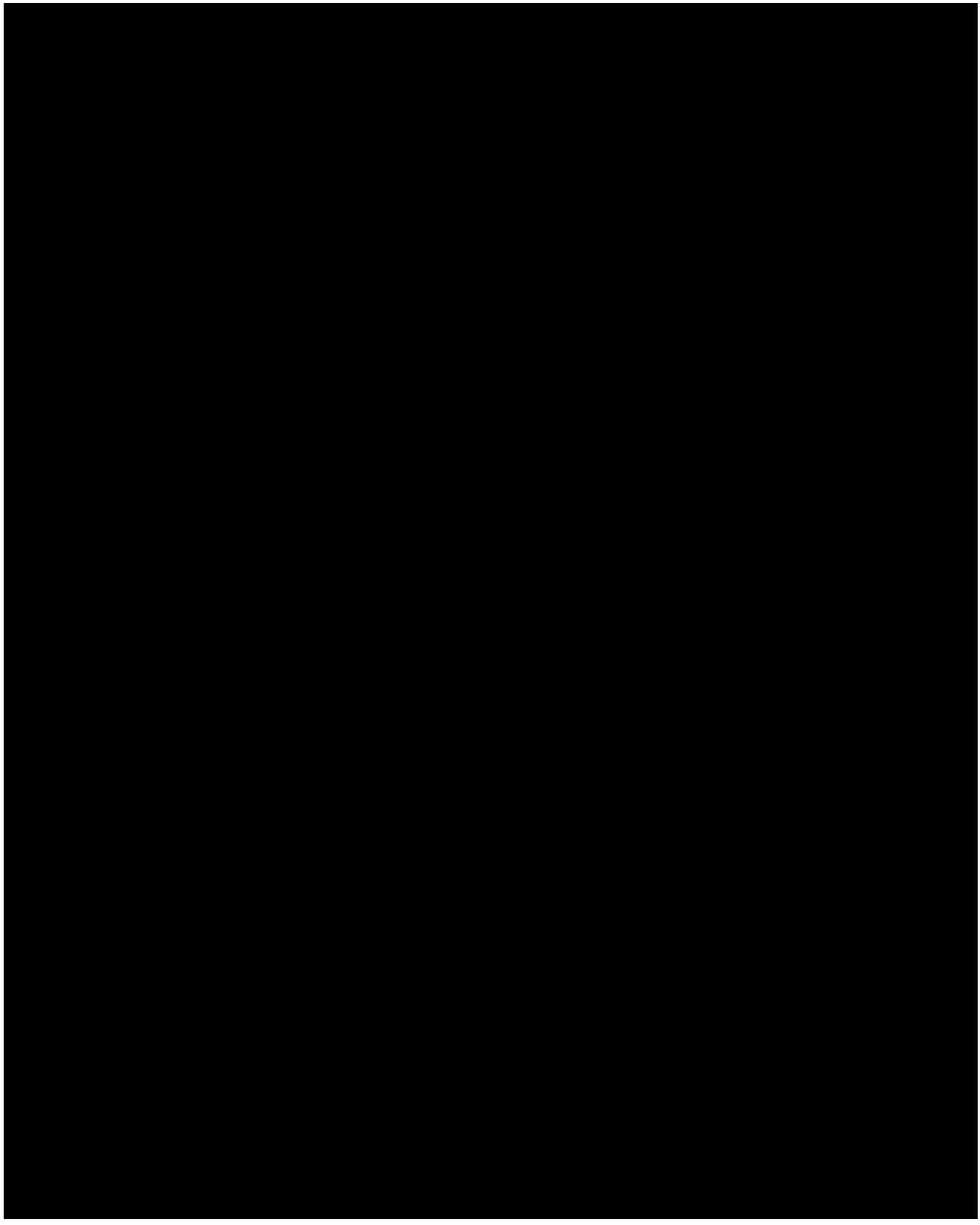








[redacted]



Appendix 5: Contraception Requirements

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the Schedule of Events.

Pregnancy test results must confirm that the subject is not pregnant.

WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A female is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.

Females in the following categories are not considered WOCBP

7. Premenarchal
8. Premenopausal with 1 of the following (i.e., permanently sterile):
    1. Documented hysterectomy
    2. Documented bilateral salpingectomy
    3. Documented bilateral oophorectomy
9. Postmenopausal

A postmenopausal state is defined as at least 12 months after last menstrual bleeding without an alternative medical cause.

In case the last menstrual bleeding cannot be clearly determined, confirmation with more than 1 follicle-stimulating hormone measurement of at least > 40 IU/L (or higher per local institutional guidelines) is required.

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated follicle-stimulating hormone measurements before study registration.

Documentation of any of these categories can come from the site personnel’s review of the female participant’s medical records, medical examination, or medical history interview.

CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

Female participants of childbearing potential are eligible for participation in the study if they agree to use a condom plus 1 of the highly effective methods of contraception listed below from the time of providing consent and until the end of relevant systemic exposure, defined as at least 60 days after final study drug administration.[a]

Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly)[b]:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable
- Other combined (estrogen- and progesterone-containing) methods
  - Vaginal ring
  - Injectable
  - Implantable
  - Intrauterine hormone-releasing system or intrauterine device
  - Bilateral tubal occlusion
- Vasectomized partner

  A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
- Sexual abstinence

  Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the product. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the subject. It is not necessary to use any other method of contraception when complete abstinence is elected.

[a] Local laws and regulations may require use of alternative and/or additional contraception methods.

[b] Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

CONTRACEPTION GUIDANCE FOR MALE PARTICIPANTS WITH PARTNER(S) OF CHILDBEARING POTENTIAL

Male participants with female partners of childbearing potential are eligible for participation in the study if they agree to the following during treatment and until the end of relevant systemic exposure defined as 60 days after final IP administration.[a]

- Inform any and all partner(s) of their participation in a clinical drug study and the need to comply with contraception instructions as directed by the Investigator;
- Use a condom;
- Must not donate sperm during 60-day period:

Female partners of male participants who have not undergone a vasectomy with the absence of sperm confirmed or a bilateral orchiectomy should consider use of effective methods of contraception. [a] Local laws and regulations may require use of alternative and/or additional contraception methods.

Birth control methods considered unacceptable:

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

Appendix 6: Creatinine Clearance

Creatinine clearance (CrCl) will be calculated using the Cockcroft-Gault formula (Cockcroft and Gault, 1976) as follows:

Females:

For serum creatinine concentration in mg/dL:

CrCl = (140 –age in years) × weight in Kg × 0.85

72 × serum creatinine in mg/dL

Males:

For serum creatinine concentration in mg/dL:

CrCl = (140 – age in years) × weight in Kg × 1.00

72 × serum creatinine in mg/dL

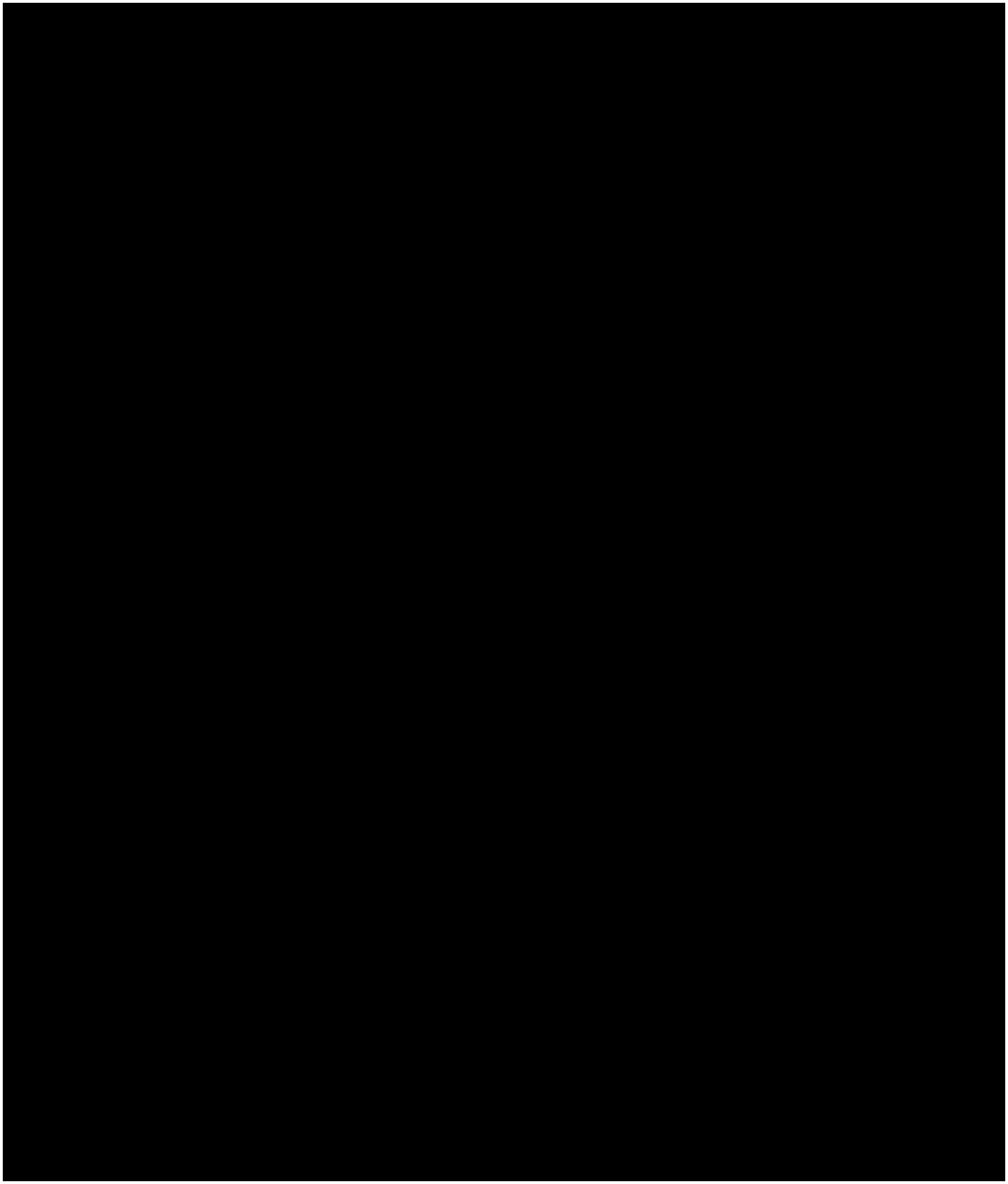
Appendix 7: Schedule of Events [redacted] (Exploratory Dose Optimization)

[redacted]

[redacted]



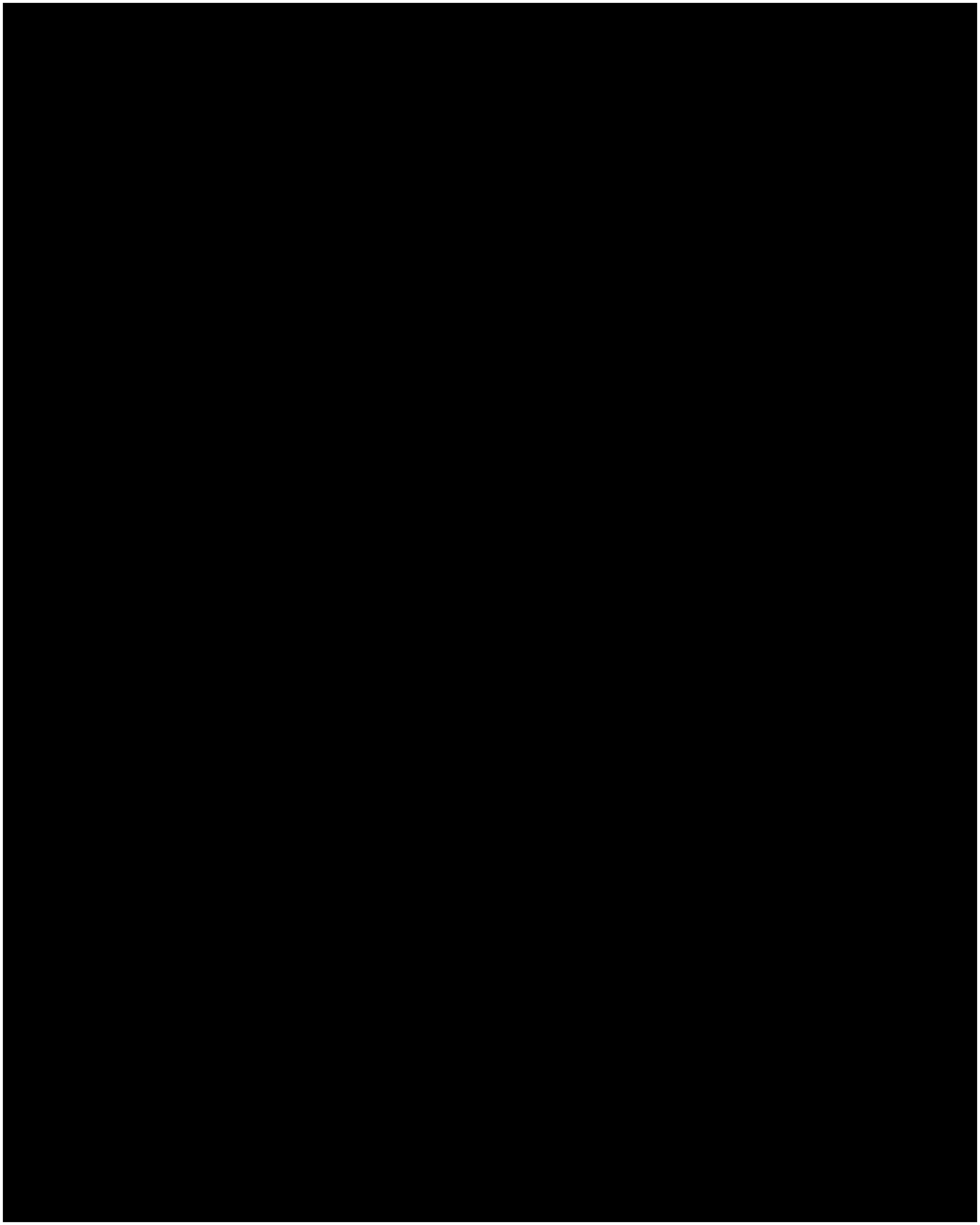
Appendix 8: Schedule of Events [redacted] (Exploratory Dose Optimization)

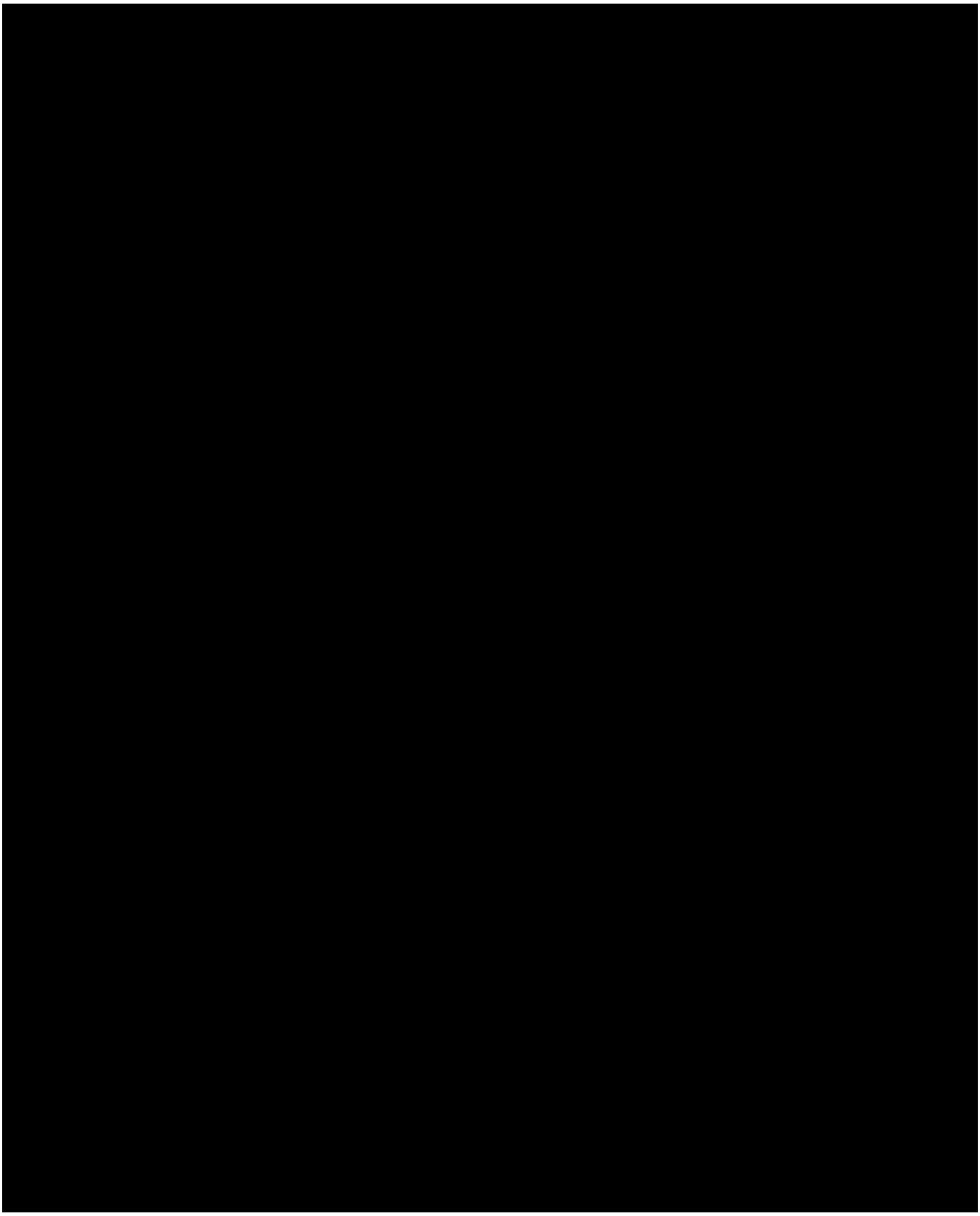


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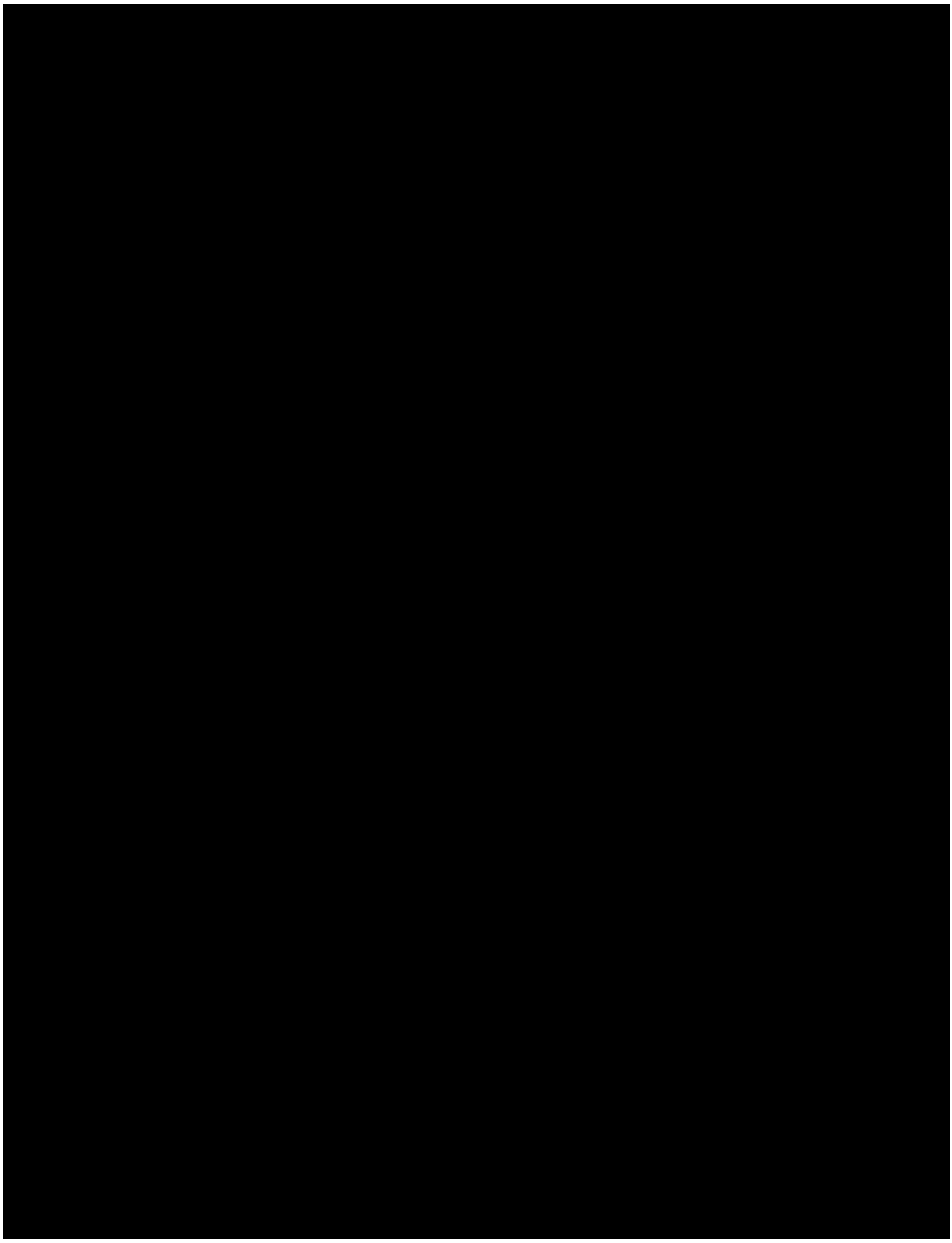


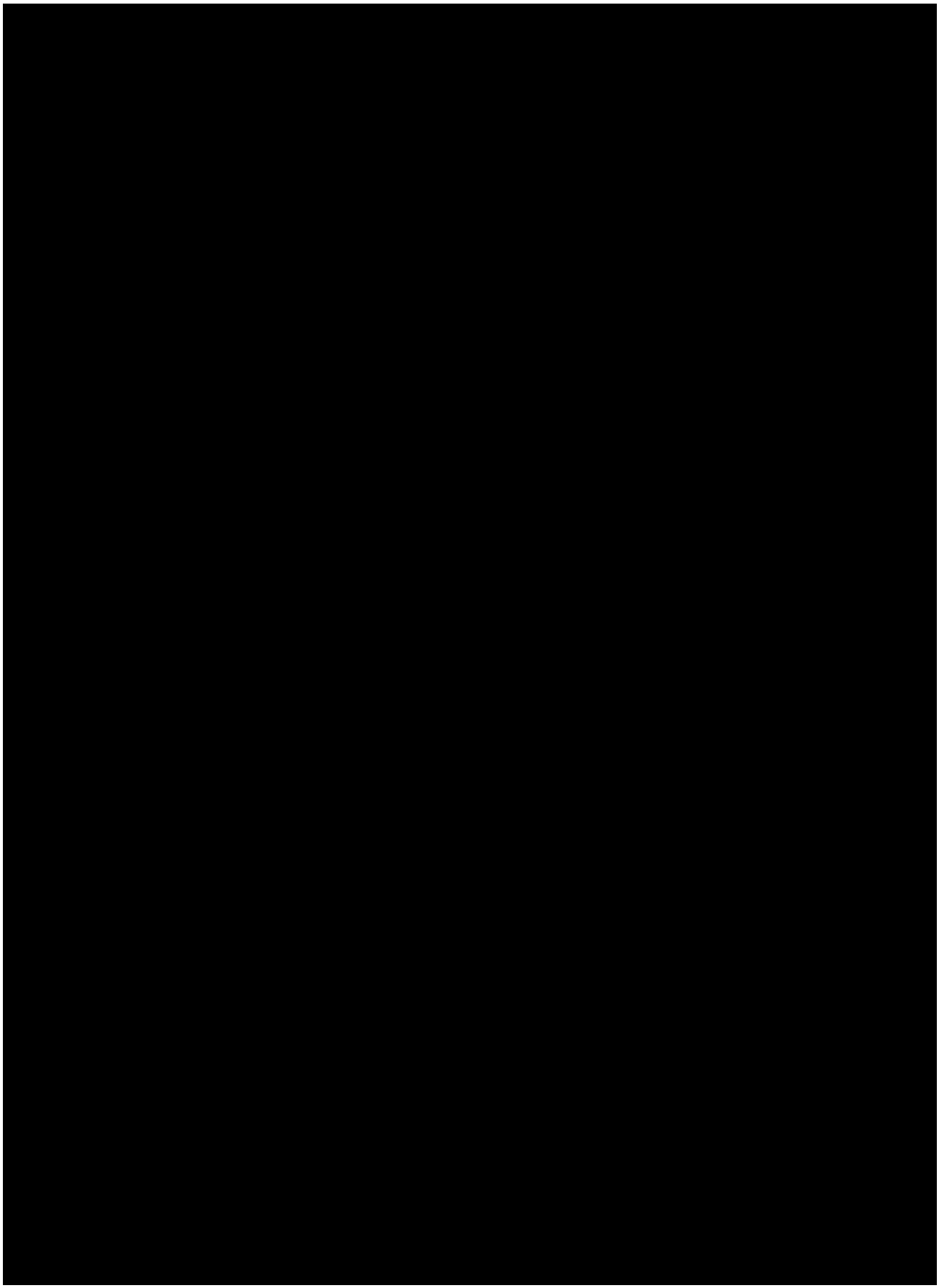
Appendix 9: Schedule of Events of [redacted] Dosing



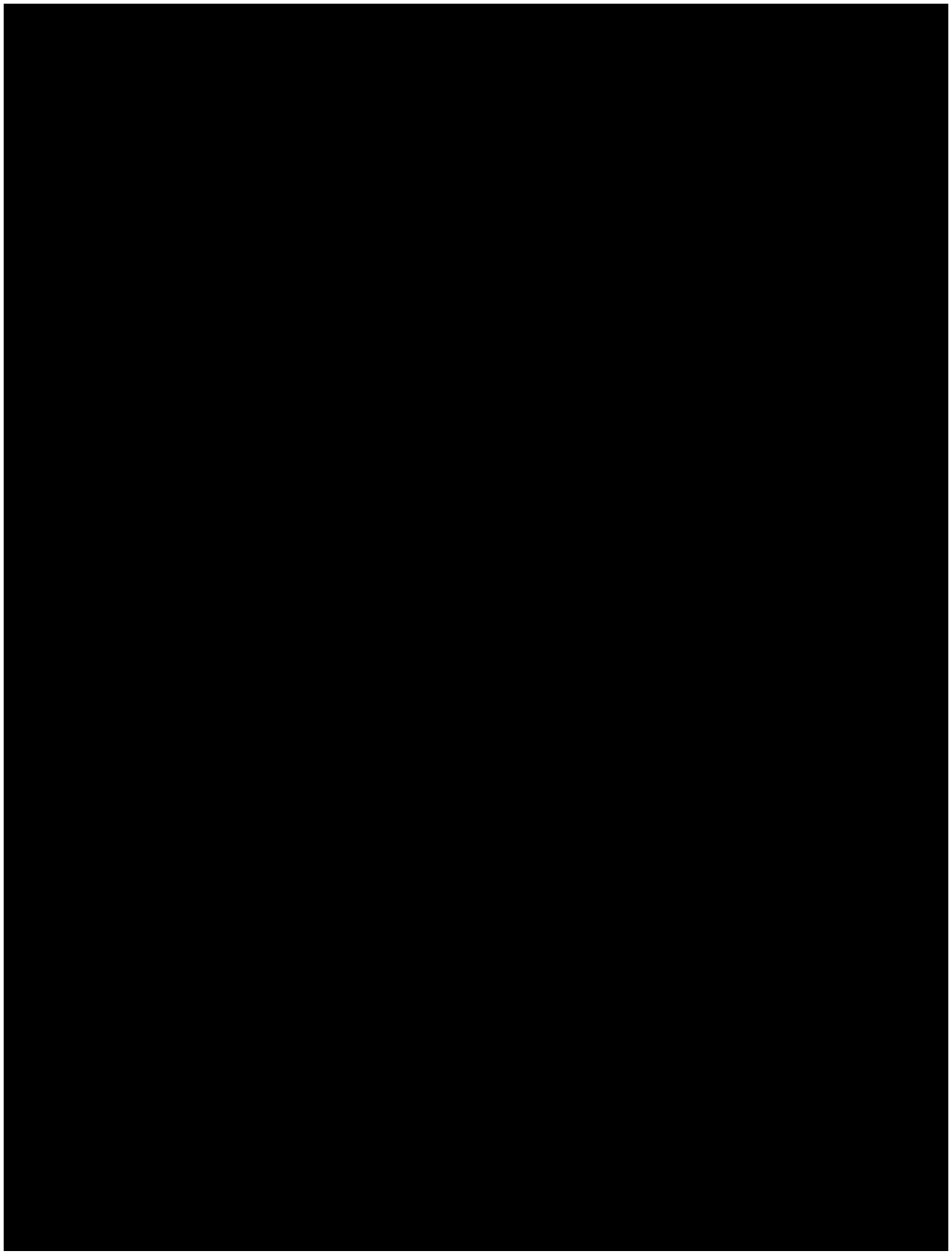


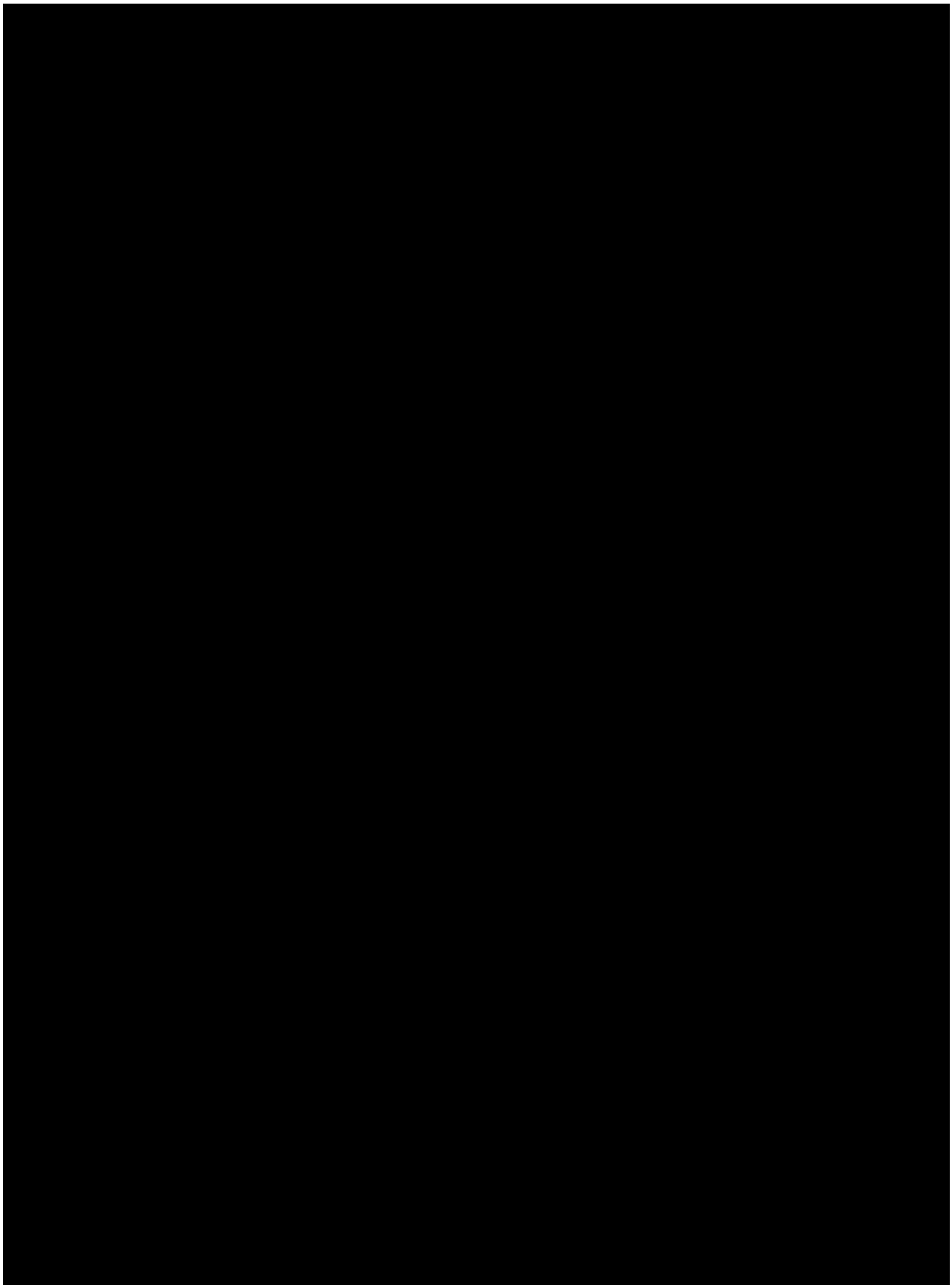
Appendix 10: Schedule of Events of [redacted] Dosing





Appendix 11: Schedule of Events of [redacted] Dosing

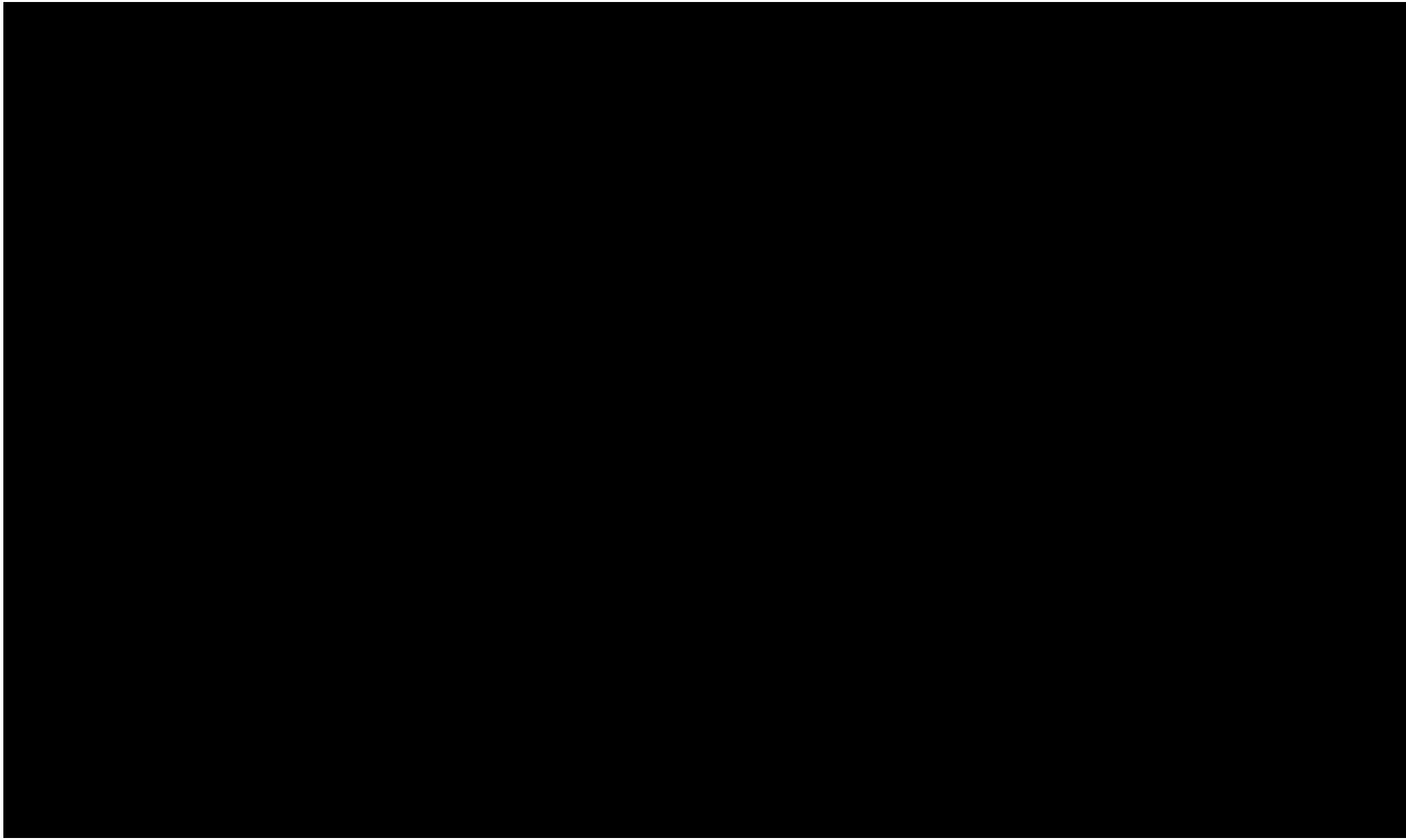






Appendix 12: Schedule of Events: Phase 2, [redacted] Dosing for [redacted] or [redacted]

[redacted]



[redacted]

[redacted]

[redacted]

;

Appendix 13: [redacted] Dose Adjustment

[redacted]

Appendix 14: General Guidelines for STAR0602 Inpatient Treatment

1. Purpose

This guideline, based on the CP-START-001 clinical protocol, is intended to offer general directions on when a participant should receive STAR0602 inpatient treatment and monitoring. It is not exhaustive, as individual participant conditions and institutional guidelines may vary. Accordingly, the investigator's judgment and discretion should take precedence.

2. Guidelines

2.1 Phase 2





2.2 Phase 2 exploratory [redacted] dosing cohorts

The [redacted] dose(s) require inpatient treatment and monitoring. The inpatient requirement for maintenance doses follow the guidelines of the monotherapy described above.

2.3 Outpatient infusion then inpatient monitoring

Based on the site's facilities, on the days of the inpatient requirement, STAR0602 can be administered as an outpatient infusion first, followed by an immediate inpatient admission to the hospital for the at least 24, up to 96hour observation period. The site will ensure that all proper precautions be taken during the infusion and the immediate transfer of the patient from the outpatient to the inpatient setting.

2.4 After transitioning from inpatient to outpatient

After transitioning from inpatient to outpatient setting, participants who receive outpatient STAR0602 administration in an appropriate ambulatory care setting should be monitored at least 1 hour post-infusion or at the investigator's discretion.

Sponsor Signatures

Study Title:	A Phase 1/2, First-in-Human, Open-Label, Dose Escalation and Expansion Study of STAR0602, a Selective T Cell Receptor (TCR)-targeting, Bifunctional Antibody-fusion Molecule, in Subjects with Unresectable, Locally Advanced, or Metastatic Solid Tumors that are Antigen-rich (START-001)
Study Number:	CP-START-001
Amendment 5.0:	18 May 2026
Original Date:	10 Aug 2022

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

The information contained in this protocol is consistent with:

- The current risk-benefit evaluation of the investigational medicinal product.
- The moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and principles of GCP as described in 21 CFR parts 50, 54, 56, 312 and ICH E6(R) and according to applicable local requirements.

The Investigator will be supplied with details of any significant or new findings related to treatment with the investigational medicinal product.



Investigator's Signature

Study Title:	A Phase 1/2, First-in-Human, Open-Label, Dose Escalation and Expansion Study of STAR0602, a Selective T Cell Receptor (TCR)-targeting, Bifunctional Antibody-fusion Molecule, in Subjects with Unresectable, Locally Advanced, or Metastatic Solid Tumors that are Antigen-rich (START-001)
Study Number:	CP-START-001
Amendment 5.0:	18 May 2026
Original Date:	10 Aug 2022

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Protocol Version History

Version	Version Date	Comments
1.0	10 Aug 2022	Original IND protocol
1.01	12 Sept 2022	Incorporating FDA review comments, submitted to FDA only. See Summary of Changes
1.02	16 Sept 2022	After IND in effect, administrative and format changes, submitted to IRBs. No Summary of Changes
2.0	25 Jan 2023	Submitted to FDA and IRBs. See Summary of Changes
2.01	03 May 2023	Submitted to FDA, Health Canada, and IRBs. See Summary of Changes
3.0	27 June 2023	Submitted to FDA, Health Canada, EU and IRBs. See Summary of Changes
3.01ANSM	20 Mar 2024	Submitted to CTIS
4.0	08 August 2024	Current version, submitted to FDA, Health Canada, EU and IRBs. See Summary of Changes
5.0	18 May 2026	Current version, submitted to FDA, Health Canada, EU and IRBs. See Summary of Changes