CLINICAL STUDY PROTOCOL

A Phase 2 Single-arm Study to Evaluate Safety and Efficacy of CRS-207 with Pembrolizumab in Adults with Previously-Treated Malignant Pleural Mesothelioma

Protocol Number:	ADU-CL-13
Version:	2.0
Date:	14 June 2017
Investigational Products:	CRS-207 (live, attenuated, double-deleted *Listeria monocytogenes* encoding human mesothelin [*Lm* Δ*actA*/Δ*inlB* hMeso]) Pembrolizumab (MK-3475)
IND Number:	13,389
Sponsor:	Aduro Biotech, Inc. 740 Heinz Avenue Berkeley, CA 94710 USA Telephone: +1 510-848-4400

2 SYNOPSIS

TITLE: A Phase 2 Single-arm Study to Evaluate Safety and Efficacy of CRS-207 with Pembrolizumab in Adults with Previously-Treated Malignant Pleural Mesothelioma

PROTOCOL NUMBER: ADU-CL-13

INVESTIGATIONAL PRODUCTS:

CRS-207 (live, attenuated, double-deleted *Listeria monocytogenes* encoding human mesothelin [*Lm* Δ*actA*/Δ*inlB* hMeso])

Pembrolizumab (MK-3475, Merck, 2014)

PHASE: 2

SITES: Up to 12 sites

INDICATION(S): Treatment of patients with malignant pleural mesothelioma (MPM) with disease progression following prior systemic chemotherapy

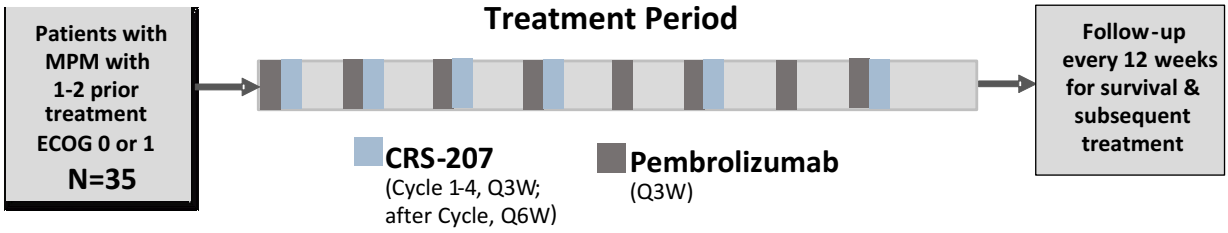
OBJECTIVES:

- Assess safety and tolerability of CRS-207 and pembrolizumab
- Evaluate the effect of CRS-207 and pembrolizumab on tumor response, pulmonary function, and survival
- Characterize the immune response following administration of CRS-207 and pembrolizumab

STUDY DESIGN:

ADU-CL-13 is a single-arm, open-label, multicenter Phase 2 study to evaluate the safety and efficacy of CRS-207 administered with pembrolizumab. The population for this study will consist of approximately 35 adults with histologically-confirmed MPM (epithelial or biphasic) whose disease has progressed after prior systemic chemotherapy. The study will consist of a Screening Period, Treatment Period (including a Safety Run-in), and a Follow-up Period.

A schematic of the study design is provided below.



ECOG = Eastern Cooperative Oncology Group; MPM = malignant pleural mesothelioma; Q*x*W = every x weeks

CRS-207 and pembrolizumab will be administered in 3-week cycles. For Cycle 1, pembrolizumab (200 mg) will be administered by intravenous infusion (IV) over 30 minutes on Day 1 and CRS-207 (starting dose 1×10^9 colony-forming units [CFU]) will be administered IV

over 1 hour on Day 2. If the infusions are well tolerated, pembrolizumab and CRS-207 will be administered on the same day (Day 1) for subsequent cycles. After 4 cycles, pembrolizumab will continue to be administered on Day 1 at each treatment cycle (every 3 weeks; Q3W); CRS-207 will be administered once every 6 weeks (i.e. every other treatment cycle; Q6W). Alternatively, study drug administration may revert back to consecutive day-dosing regimen as performed in Cycle 1 (Day 1 pembrolizumab and Day 2 CRS-207).

Treatment cycles with pembrolizumab will continue for up to 35 cycles as long as there is adequate safety and potential for clinical benefit. After cycle 35, subjects may receive CRS-207 monotherapy if subject meets dosing eligibility, is clinically stable, and the subject is deriving clinical benefit. If radiographic disease progression is observed, clinically stable subjects who meet dosing eligibility may continue to receive CRS-207 and pembrolizumab at the discretion of the Investigator. Subjects who experience unacceptable toxicity(ies) related to either CRS-207 or pembrolizumab may continue on study and receive CRS-207 or pembrolizumab monotherapy with approval from medical monitor. Subjects who experience unacceptable toxicity(ies) related to both CRS-207 and pembrolizumab in Cycle 1 should be discontinued from the treatment. However, if in the opinion of the investigator, the subject is deriving clinical benefit from the study treatment, the subject may be allowed to continue with treatment after discussion with the Medical Monitor.

A Safety Run-in will be completed since there are no precedent data on the use of pembrolizumab with CRS-207. Treatment of the first 6 subjects will be staggered, with no more than 1 subject treated per week; subjects will be monitored for unacceptable toxicity(ies) during the first 28 days (at least through 7 days after the Cycle 2 dose). During the Safety Run-in, evaluable subjects are defined as those who remain on study for the 28-day monitoring period, subjects with unacceptable toxicity, and subjects who are discontinued for safety reasons at the Investigator's discretion (even if criteria for unacceptable criteria are not met). The medical monitor and participating investigators will review all unacceptable toxicities on an ongoing basis and determine if the Safety Review Team should meet ad hoc to evaluate further. In the event 2 subjects in the first 6 treated experience unacceptable toxicity(ies), the Safety Review Team will be convened to determine if the dose of CRS-207 will be reduced in subsequently enrolled subjects in half-log increments.

Safety data including all unacceptable toxicities will be reviewed by a Safety Review Team comprised of participating investigators in the study, the Medical Monitor, and representatives of the Sponsor. Once the Safety Run-in period is complete, safety will continue to be evaluated on an ongoing basis in this open-label study. Cumulative clinical experience with CRS-207 and pembrolizumab will be used to assess whether adverse events (AEs) are considered expected. If >33% of subjects dosed experience unacceptable toxicity(ies) attributable to study drug(s), the Safety Review Team will be convened to determine if dosing will be suspended. The schedule of events is provided in Table 2-1 or Table 2-2 for subjects who experience tolerability issues and continue to follow the consecutive-day dosing regimen). Tumor imaging and pulmonary function will be assessed at baseline (Screening) and during the Treatment Period approximately every 6 weeks starting at Cycle 3. Tumor measurement and assignment of response will be determined by local Investigators using the modified response evaluation criteria in solid tumors (modified RECIST) for MPM (Byrne, 2004). If radiographic disease progression is observed, another scan should be done at least four weeks later to confirm disease progression prior to treatment discontinuation. Peripheral blood will be collected to assess immune responses

directed against *L. monocytogenes*, mesothelin, and other tumor-associated antigens. Paired tumor biopsies will be collected at Screening and during Cycle 2 to explore the association of programmed death receptor ligand-1 (PD-L1) expression and tumor-infiltrating lymphocyte characteristics with clinical responses. Blood will be collected at End of Treatment (EOT) to assess clearance of CRS-207 and at [redacted]

The Treatment Period is defined as the time from the first dose of study drug administration until discontinuation of both CRS-207 and pembrolizumab and completion of an End of Treatment (EOT) visit. All subjects must complete an End of Treatment (EOT) visit no more than four weeks following the final dose of study drug and/or prior to receipt of other cancer-related treatment. Subjects will be administered antibiotics beginning at the EOT visit to eliminate any potentially residual CRS-207. At the end of the Treatment Period, subjects will enter the Follow-up Period of the study and will be followed for survival and subsequent cancer-related therapies every 3 months until death or close of study by the Sponsor. Sites will attempt to obtain vital status data from public records or other external sources where possible if a subject withdraws consent from study (i.e. refuse follow-up for vital status) or is documented as lost to follow up.

INCLUSION AND EXCLUSION CRITERIA:

Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1. Histologically-confirmed epithelial or biphasic MPM; biphasic tumors must have a predominantly (≥50%) epithelial component
2. No more than 2 prior lines of anti-cancer therapy, one of which must have included pemetrexed and a platinum. Documented radiographic progression of disease after treatment with pemetrexed and a platinum is required.
3. Measurable disease as defined by modified RECIST for MPM
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
5. Adequate organ and marrow function at Screening, as defined by:
    - White blood cell count ≥ 3000/ μL
    - Absolute neutrophil count ≥ 1500/μL
    - Absolute lymphocyte count ≥ 800/μL
    - Platelet count ≥ 100,000/μL
    - Bilirubin ≤ 1.5 × institutional upper limit of normal (ULN), or ≤ 3 × institutional ULN if due to Gilbert's disease
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × institutional ULN or ≤ 5 × ULN for subjects with liver metastases
    - Albumin ≥ 3.0 g/dL
    - Serum creatinine ≤1.5 × institutional ULN
    - Hemoglobin ≥ 9.0 g/dL

- International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN and activated partial thromboplastin time (aPTT) ≤1.5 × ULN (if receiving anticoagulant therapy, values should be within therapeutic range of intended use)

Any Grade 3 or higher abnormality in any serum chemistry or hematology parameter must be discussed and approved by the Medical Monitor prior to enrollment (even if considered not clinically significant)

6. Aged 18 years and over
7. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) ≥ 45% of predicted value as measured by spirometry; and oxygen saturation ≥ 90% on room air as measured by pulse oximeter
8. Women of childbearing potential (WOCBP) and fertile males with WOCBP partners must use highly effective contraception [per (CTFG, 2014)] throughout the Treatment Period (from first dose and through 120 days after final dose of study drug). Contraception must include at least one barrier method to minimize risk of fluid transmission.
9. Provide written informed consent and is willing and able to comply with all study procedures.

Exclusion Criteria

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

1. Pleurodesis within 14 days prior to first dose of study drug
2. Has a diagnosis of immunodeficiency, receiving TNF pathway inhibitors, PI3 kinase inhibitors, chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug
3. Active second malignancy with the exception of any of the following:
   - Adequately treated basal cell carcinoma
   - Squamous cell carcinoma of the skin, or *in situ* cervical cancer
   - Low-risk prostate cancer (i.e. Gleason score < 7 and prostate specific antigen < 10 ng/mL); or
   - Any other cancer from which the individual has been disease-free for ≥ 3 years
4. Untreated or unstable brain metastases. Individuals with treated (surgically excised or irradiated) and stable brain metastases are eligible as long as the subject has adequately recovered from treatment and the treatment was ≥ 28 days prior to first dose of study drug. A baseline brain computed tomography (CT) with contrast or magnetic resonance imaging (MRI) within 14 days prior to first dose of study drug must be negative for new brain metastases.
5. Prior anti-cancer monoclonal antibody within 4 weeks prior to first dose of study drug, or not recovered from adverse effects due to agents administered more than 4 weeks earlier
6. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks

prior to first dose of study drug

7. Ongoing adverse effects (i.e. ≤ Grade 1 or at baseline) due to a previously administered anti-cancer agent. Individuals with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion.
8. History of (non-infectious) pneumonitis that required steroids or current pneumonitis
9. History of interstitial lung disease
10. Received transfusion of blood products (including platelets or red blood cells) or administration of colony-stimulating factors (including G-CSF, GM-CSF or recombinant erythropoetin) within 4 weeks prior to first dose of study drug
11. Active infection requiring systemic therapy
12. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or agents targeting other checkpoint pathways (e.g. CTLA-4)
13. Prior immunotherapy with CRS-207 or any other *Listeria*-based agent, therapeutic cancer vaccine, or adoptive T cell immunotherapy
14. Received any prophylactic vaccine within 14 days of first dose of study drug or received a live vaccine within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted.
15. Participated in any other study in which receipt of an investigational new drug, or investigational device occurred within 28 days of first dose of study drug
16. Clinically significant heart disease (such as uncontrolled angina, myocardial infarction within 3 months of study initiation, congestive heart failure, or New York Heart Association Class III or IV heart failure)
17. Known valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis
18. Known allergy to <u>both</u> penicillin and sulfa drugs
19. Known or suspected allergy or hypersensitivity to yeast or any other component of CRS-207 (e.g. glycerol) or pembrolizumab; or history of severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.
20. History of autoimmune disease that has required systemic treatment in the past 2 years, including:
    - Inflammatory bowel disease (including ulcerative colitis and Crohn's Disease)
    - Rheumatoid arthritis
    - Systemic progressive sclerosis (scleroderma)
    - Systemic lupus erythematosus
    - Autoimmune vasculitis (e.g. Wegener's granulomatosis)
    - Central nervous system or motor neuropathy considered of autoimmune origin (e.g. Guillain-Barré syndrome, myasthenia gravis, multiple sclerosis)

    Individuals with vitiligo, moderate to severe psoriasis, Sjogren's Syndrome, interstitial

cystitis, Graves' or Hashimoto's Disease, celiac disease, diabetes mellitus type 1, or hypothyroidism stable on hormone replacement may be allowed with Medical Monitor approval.

21. Received a diagnosis of human immunodeficiency virus (HIV)
22. Received a diagnosis of hepatitis B, or hepatitis C for which there is no clear evidence of natural immunity, immunity subsequent to vaccination, or successful eradication of the virus following antiviral therapy (individuals who are hepatitis C antibody positive may be enrolled if negative viral load confirmed at Screening)
23. If WOCBP, pregnant or breastfeeding; negative pregnancy status must be confirmed within 24 hours of first dose of study drug.
24. Implanted medical devices that pose high risks for colonization and cannot be easily removed (e.g., artificial heart valves, pacemakers, prosthetic joints, orthopedic screw(s), metal plate(s)) if infection occurs. Other common devices such as venous access devices (e.g., Port-a-Cath or Mediport) may be permitted as well as arterial and venous stents and dental and breast implants that were placed more than 3 months prior to first dose of study drug.
25. Major surgery or significant traumatic injury occurring within 28 days prior to first dose of study drug. If major surgery occurred > 28 days prior to first dose of study drug, individual must have recovered adequately from the toxicity and/or complications from the intervention prior to the first dose of study drug.
26. Unhealed wound or ulcer; or a bone fracture considered non-healing
27. History or evidence of inherited bleeding diathesis or coagulopathy
28. Unable or unwilling to withhold or discontinue any prohibited or restricted medications/procedures for the specified periods during the study
29. Intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements, or in the Investigator's assessment would place the subject at an unacceptable risk for study participation.

DURATION OF SUBJECT PARTICIPATION:

The Screening Period may last up to 28 days. During the Treatment Period, a subject may continue to receive study drugs after documented progression provided dosing eligibility criteria are satisfied, and the investigator thinks the subject may be benefitting from continued treatment. Pembrolizumab may be administered up to a maximum of 35 cycles. After cycle 35, subjects may receive CRS-207 monotherapy if subject meets dosing eligibility, is clinically stable, and the subject is deriving clinical benefit. Discontinuation may occur due to unexpected clinical significant adverse event, lack of clinical benefit as determined by the investigator, withdrawal of consent by the subject, or termination of the study by the Sponsor. At the end of the Treatment Period, subjects will enter the Follow-up Period and will be followed for survival and subsequent cancer-related therapy every 3 months until death or close of study by the Sponsor. [redacted]

DOSAGE FORMS AND ROUTE OF ADMINISTRATION:

CRS-207 is formulated as 1×10^9 CFU suspended in [redacted], filled into a single-use 2-mL glass vial with a gray butyl stopper and aluminum crimp seal with a flip off cap. 1.0 mL of CRS-207 is diluted in sterile saline and administered by IV infusion over approximately 1 hour.

Pembrolizumab for injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution. Each vial contains 100 mg/4 mL (25 mg/mL) solution in a single-use vial. Each 1 mL of solution contains 25 mg of pembrolizumab formulated in L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP. Pembrolizumab will be diluted in sterile saline and administered at a dose of 200 mg via IV infusion over 30 minutes.

EFFICACY VARIABLES:

Tumor measurements will be performed by radiologic evaluation (CT). All tumor response variables will be assessed by the Investigator using modified RECIST for MPM. Pulmonary function will be assessed by spirometry.

Primary Efficacy Variable:

- Objective response rate (ORR), defined as the proportion of subjects with complete response (CR) or partial response (PR)

Secondary Efficacy Variables:

- Disease control rate (DCR), defined as the percentage of subjects with CR, PR, or stable disease (SD)
- Progression-free survival (PFS) defined as time from first dose of study drug until disease progression or death
- Proportion of subjects with improvement in pulmonary function (FVC), defined as an increase from baseline of either ≥400 mL or ≥20% assessed using spirometry
- Overall survival (OS), as measured from date of first dose of study drug until death

SAFETY VARIABLES:

Safety will be assessed by collection of data on AEs, clinical laboratory assessments, ECOG performance status, vital signs, weight, physical examination, electrocardiogram (ECG) parameters, concomitant medications, and testing blood for CRS-207 clearance.

STATISTICAL ANALYSES:

Descriptive summaries for categorical variables will include counts and percentages. Descriptive summaries for continuous variables will include means, medians, standard deviations and minimum and maximum values. Descriptive summaries of time to event data will include medians and confidence intervals. Graphical summaries of the data may be presented. All data will be listed for all subjects. Further details of the analysis, including the handling of missing data, transformations, other data handling procedures, and analytical methodology will be

provided in the Statistical Analysis Plan (SAP). Exploratory analyses of the data will be conducted as deemed appropriate.

All analyses of efficacy and safety will be performed on all subjects who were enrolled and received at least one dose of study drug.

Efficacy Analyses

For the primary efficacy analysis, ORR is defined as the proportion of subjects with PR or CR according to modified RECIST for MPM. Subjects who discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered as non-responders. Subjects who discontinue for other reasons prior to post-baseline tumor assessments will be replaced and will not be included in the primary efficacy analysis.

Secondary efficacy variables will be calculated for all subjects who receive at least one dose of study drug and are evaluable for response.

The primary definition for objective disease response and disease progression will be determined by the Investigator using modified RECIST for MPM. Additional supportive analyses may be performed separately by an independent reviewer using objective disease responses definitions based on RECIST v1.1 and/or immune related response criteria (irRC).

Safety Analyses

AEs will be coded according to MedDRA version 18.1 or higher and assessed for severity using the NCI-CTCAE v. 4.03. AEs will be summarized by system organ class and preferred term and presented in decreasing order of frequency.

Changes in vital signs, ECG data, hematology, serum chemistry, and urinalysis parameters from baseline to the EOT will be examined. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified. Laboratory data will be summarized for each time-point that specimens are collected. Changes in NCI toxicity grading will be presented using shift tables and listings of clinically significant values.

SAMPLE SIZE DETERMINATION:

The sample size is based on an A'Hern single-stage phase 2 design (A'Hern, 2001). A sample size of 35 evaluable subjects are required to decide whether the proportion responding is less than or equal to 0.21 or greater than or equal to 0.40. If the number of responses is 12 or more, the hypothesis that $P \leq 0.21$ is rejected with a target error rate of 0.05 (alpha). If the number of responses is 11 or less, the hypothesis that $P \geq 0.40$ is rejected with a target error rate of 0.20 (power = 0.80).

Table 2-1 Schedule of Events: Same-day (D1) Dosing Regimen[1]

	Screen	Treatment Period															EOT[3]	Follow-up
		Cycle 1				Cycle 2				Cycle 3			Cycle 4		Cycles 5 and Beyond		Within 4 Weeks Post Final Dose	[redacted]
															Odd Numbered Cycles (5, 7, etc.)	Even Numbered Cycles (6, 8, etc.)		
Study Day[2]	**-28 to 0**	**1**	**2**	**3**	**9**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**1**	**2**	**1**	**1**	**-**	**-**
Visit Window (Days)	**-**	**-3**	**-**	**-**	**±1**	**±3**	**-**	**±1**	**±1**	**±3**	**-**	**±1**	**±3**	**-**	**±3**	**±3**	**-3**	**±7**
Study Procedures																		
Informed Consent	X																	
Inclusion/Exclusion; Enrollment Form[4]	X																	
Medical and Medication History, Height[5]	X																	
Biopsy[6]	X							X										
Archived Tumor Tissue[7]		X																
CT Tumor Evaluation[8]	X									X					X		X	
Pulmonary Function Test[9]	X									X					X		X	
Electrocardiogram, 12-lead[10]	X	X	X			X											X	
ECOG Performance Status	X	X				X				X			X		X	X	X	
Physical Examination and Weight[11]	X	X				X				X			X		X	X	X	
Vital Signs[12]	X	X	X	X		X	X			X	X		X	X	X	X	X	
Pulse Oximetry[12]	X	X				X				X			X		X	X	X	
Adverse Event		X	X	X	X	X	X	X	X	X	X	X	X	X	X[13]	X[13]	X	
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X[13]	X[13]	X	
Survival Follow-up Contact[14]																		X
Clinical Laboratory Sample Collection[15]	***Central lines must not be accessed for blood collection or for any reason during or within 4 days of CRS-207 infusion***																	
Virology Screen[16]	X																	
Hematology and Chemistry[17]	X	X	X	X		X	X			X	X		X	X	X	X	X	
Coagulation Panel[18]	X		X	X		X	X										X	
Urinalysis[19]	X	X				X				X			X		X	X	X	
Thyroid Function Test[20]	X	X								X					X		X	
Pregnancy Test[21]	X					X				X			X			X		

	Screen	Treatment Period															EOT[3]	Follow-up
		Cycle 1				Cycle 2				Cycle 3			Cycle 4		Cycles 5 and Beyond		Within 4 Weeks Post Final Dose	[redacted]
															Odd Numbered Cycles (5, 7, etc.)	**Even** Numbered Cycles (6, 8, etc.)		
Study Day[2]	**-28 to 0**	**1**	**2**	**3**	**9**	**1**	**2**	**8**	**15**	**1**	**2**	**8**	**1**	**2**	**1**	**1**	**-**	**-**
Visit Window (Days)	**-**	**-3**	**-**	**-**	**±1**	**±3**	**-**	**±1**	**±1**	**±3**	**-**	**±1**	**±3**	**-**	**±3**	**±3**	**-3**	**±7**
Research Sample Collection	***Central lines must not be accessed for blood collection or for any reason during or within 4 days of CRS-207 infusion***																	
CD4 and CD8 Counts[22]		X																
HLA typing[22]		X																
Serum/Plasma for Immune Monitoring[23]		X	X	X	X	X	X	X		X	X	X	X	X	X		X	
Whole Blood for PBMC[24]		X			X	X		X		X		X	X		X		X	
Blood for CRS-207 Surveillance[25]																	X	X
Study Medication																		
Pembrolizumab[1, 13, 26]		X				X				X			X		X	X		
CRS-207[1, 13, 27, 28]			X			X				X			X			X		
Antibiotics (with diary)[29]																	X	
Subset Studies (select sites only)																		
CRS-207 Clearance/Shedding			X[30]			X[30]												

Table 2-2: Schedule of Events: Consecutive-day (Day 1 and 2) Dosing Regimen (for Subjects with Tolerability Issues)[1]

	Treatment Period																EOT[3]	Follow-up
	Cycle 2					Cycle 3				Cycle 4				Cycles 5 and Beyond			Within 4 Weeks Post Final Dose	[redacted]
														Odd Numbered Cycles (5, 7, etc.)	Even Numbered Cycles (6, 8, etc.)			
Study Day[2]	**1**	**2**	**3**	**9**	**15**	**1**	**2**	**3**	**9**	**1**	**2**	**3**	**9**	**1**	**1**	**2**	**-**	**-**
Visit Window (Days)	**±3**	**-**	**-**	**±1**		**±3**	**-**	**-**	**±1**	**±3**	**-**	**-**	**±1**	**±3**	**±3**	**-**	**-3**	**±7**
Study Procedures																		
Biopsy[6]				X														
CT Tumor Evaluation[8]						X								X			X	
Pulmonary Function Test[9]						X								X			X	
Electrocardiogram, 12-lead[10]	X	X															X	
ECOG Performance Status	X					X				X				X	X		X	
Physical Examination and Weight[11]	X					X				X				X	X		X	
Vital Signs[12]	X	X	X			X	X	X		X	X	X		X	X	X	X	
Pulse Oximetry[12]	X					X				X				X	X		X	
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X[13]	X	X[13]	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X[13]	X	X[13]	X	
Survival Follow-up Contact[14]																		X
Clinical Laboratory Sample Collection[15]	***Central lines must not be accessed for blood collection or for any reason during or within 4 days of CRS-207 infusion***																	
Hematology and Chemistry[17]	X	X	X			X	X	X		X	X	X		X	X	X	X	
Coagulation Panel[18]	X	X	X														X	
Urinalysis[19]	X					X				X				X	X		X	
Thyroid Function Test[20]						X								X			X	
Pregnancy Test[21]	X					X				X					X			
Research Sample Collection	***Central lines must not be accessed for blood collection or for any reason during or within 4 days of CRS-207 infusion***																	
Serum/Plasma for Immune Monitoring[23]	X	X	X	X		X	X	X	X	X	X	X		X			X	
Whole Blood for PBMC[24]	X			X		X			X	X				X			X	
Blood for CRS-207 Surveillance[25]																	X	X
Study Medication																		
Pembrolizumab[1, 13, 26]	X					X				X				X	X			
CRS-207[1, 13, 27, 28]		X					X				X					X		
Antibiotics (with diary)[29]																	X	
Subset Studies (select sites only)																		
CRS-207 Clearance/Shedding[30]		X	X	X														

FOOTNOTES FOR TABLE 2-1 AND TABLE 2-2

[1] CRS-207 and pembrolizumab will be administered in 3-week cycles. For Cycle 1, pembrolizumab will be administered on Day 1 and CRS-207 on Day 2. If the infusions are well tolerated, pembrolizumab and CRS-207 may be administered on the same day (Day 1) for subsequent cycles. After 4 cycles, pembrolizumab will continue to be administered on Day 1 at each treatment cycle every 3 weeks; CRS-207 will be administered once every 6 weeks. If there is intolerance to same day dosing, study drug administration may revert back to consecutive day-dosing regimen as performed in Cycle 1 during the Safety Run-in Period (Table 2-2). Treatment cycles with pembrolizumab will continue for up to 35 cycles as long as there is adequate safety and potential for clinical benefit.

[2] At visits where dosing is indicated, all assessments should be completed prior to dosing unless stated otherwise. If any doses are delayed, adjust subsequent dosing schedule accordingly.

[3] **EOT Visit** will occur within 4 weeks after the final dose of study drug or prior to start of subsequent cancer-related therapy. If the EOT visit occurs earlier than 4 weeks, a safety follow-up contact on Day 28 (-3 days) is required to complete the AE reporting period; document contact in the study records. After the EOT Visit, the subject will be followed [redacted]

[4] **Enrollment form** must be signed by principal investigator or sub-investigator confirming eligibility. The completed/signed enrollment form and redacted source records (CT scan report confirming progression on prior treatment) must be faxed to number provided in the Study Reference Manual for approval by Sponsor and/or designee. Subjects must initiate treatment within 2 weeks of approved enrollment.

[5] **Height** is measured without shoes.

[6] **Biopsy (pre- and post-treatment):** Image-assisted core needle biopsy must be obtained at any accessible tumor site (primary preferred, metastatic site acceptable); fine needle aspirations are not acceptable. Baseline biopsy must be performed after subject eligibility is confirmed and must NOT be performed on the same day as pembrolizumab or CRS-207 administration. Post-treatment biopsy must be performed between day 8-15 post-Cycle 2 CRS-207 infusion and 7 days prior to Cycle 3. Collect serum/plasma and whole blood for PBMC on same day as post-treatment biopsy. If unscheduled biopsies are performed while subject is on treatment, retain a sample for Sponsor research purposes. Biopsy collection and processing instructions are provided in the Laboratory Manual.

[7] **Archived tumor tissue**: Refer to Laboratory Manual for additional instructions.

[8] **CT scan** of the thorax and abdomen. If CT contraindicated, an MRI should be performed. If subject has history of treatment for brain metastases, a baseline brain CT with contrast or MRI within 14 days prior to first dose of study drug must be negative for new brain metastases. CT scans must be done at Screening and up to 7 days prior to dosing every other cycle starting at Cycle 3 (e.g. Cycles 3, 5, 7, etc.). CT scans should follow the calendar and shouldn't be adjusted for dose delays. Tumor measurement and response assessment will be done per modified RECIST for MPM. If radiographic disease progression is observed, another scan should be done at least 4 weeks later to confirm the disease progression prior to treatment discontinuation. Sites must submit a copy of each scan on CD or other image media to the Sponsor; all protected health information (e.g. name, medical record number, etc.) must be redacted. Instructions for submission of scans are provided in the Study Reference Manual.

[9] **Pulmonary function tests** (spirometry) for FVC and FEV_1 performed at Screening and up to 7 days prior to dosing every other cycle starting at Cycle 3 (e.g. Cycles 3, 5, 7, etc.).

[10] **Electrocardiogram:** Perform routine 12-lead ECGs after the subject has rested in a supine position for ≥5 minutes. During Cycles 1 and 2 obtain ECG [heart rate, PR interval, QT interval, QRS duration, QTcF (Fridericia's correction), and QTcB (Bazett's correction)] (collected within approximately a 5-minute window) prior to, immediately after and 1 hour following each pembrolizumab and CRS-207 dose. If abnormal at 1-hour post-infusion, repeat until baseline achieved. Additional ECGs may be performed if clinically indicated.

[11] Complete **physical examination** at Screening and EOT; symptom-directed physical examination at all other indicated visits (up to 3 days prior to dosing).

[12] At visits indicated obtain **vital signs** (blood pressure, pulse, respiratory rate, and temperature) and **pulse oximetry**. For each pembrolizumab infusion obtain vital signs pre- and post-infusion. For each CRS-207 infusion obtain vital signs pre- and every 30 minutes during CRS-207 infusion and every hour during observation period. Pulse oximetry may be obtained if clinically indicated.

[13] At Cycle 5 and beyond, follow-up contact for **AEs and concomitant medications** will be conducted 1 day after pembrolizumab and CRS-207 infusion. Document contact in the study records.

[14] **Survival follow-up:** Subjects will be contacted every 3 months to collect survival and subsequent cancer-related treatments in the Follow-up Period. Document contact in the study records. Blood will continue to be collected for CRS-207 surveillance at [redacted]

[15] **Clinical Laboratory Samples** may be collected and tested up to 3 days prior to dosing.

[16] **Virology** screen includes HIV antibody, hepatitis B surface antigen, and hepatitis C antibody; additional virology may also be evaluated. Subjects who are hepatitis C antibody positive and confirmed negative viral load at Screening will be considered eligible.

[17] **Hematology:** complete blood count (WBC, red blood cells, hematocrit, and hemoglobin) with differential including ANC, ALC and platelet count
Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, ALT, AST, alkaline phosphatase, bilirubin (total, direct, indirect), total protein, albumin, calcium, magnesium, uric acid, and phosphate.

[18] **Coagulation panel:** PT, INR, aPTT, D-dimers, fibrinogen collected during Cycles 1 and 2 prior to and 1-day post-CRS-207 infusion. Additional samples for coagulation panel may be collected as clinically indicated.

[19] **Urinalysis:** bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity (with microscopy at Screening and EOT)

[20] **Thyroid panel:** triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH)

[21] **Pregnancy tests** administered to WOCBP only: serum HCG is required at Screening; urine pregnancy tests allowed at subsequent time points. In case of delayed menstrual period (> 1 month) confirm absence of pregnancy prior to dosing.

[22] **CD4 and CD8 Counts** and **HLA typing** are performed by central laboratory. Instructions for collection of the samples is provided in the Laboratory Manual. If HLA sample is rejected for analysis, an additional sample may be collected at a later time point

[23] **Immune monitoring:** collect serum and plasma at visits indicated pre-pembrolizumab, pre-CRS-207(collect only if not same day dosing), and 18-24 hours and 7 days post-CRS-207. At Cycle 2, blood for immune monitoring for the 7 days post CRS-207 infusion should be taken on same day as post-treatment biopsy (Day 8-15). Cycle 5 and beyond (at all Odd Numbered Cycles): collect blood prior to pembrolizumab infusion. Refer to Laboratory Manual for collection and processing requirements.

[24] **Whole blood for PBMC:** At Cycle 2, blood for PBMC for the 7 days post CRS-207 infusion should be taken on same day as post-treatment biopsy (Day 8-15). Cycle 5 and beyond (at all Odd Numbered Cycles): collect blood prior to pembrolizumab infusion. Refer to Laboratory Manual for collection and processing requirements.

[25] At EOT, blood for **CRS-207 surveillance** will be collected prior to initiation of antibiotics (if applicable, blood must also be collected through the central line port) to assess CRS-207 clearance. After EOT, blood will continue to be collected for CRS-207 surveillance at [redacted]. AESI will continue to be reported in the follow-up period (refer to Section 8.4)

[26] **Pembrolizumab** will be administered at indicated cycles via IV infusion over approximately 30 minutes (at cycles with same-day dosing, pembrolizumab is administered first followed by CRS-207 infusion). Obtain vital signs (BP, pulse, respiratory rate, temperature) prior to, and immediately following each pembrolizumab infusion. If subjects on same-day dosing schedule experience severe infusion-related reactions related to the pembrolizumab infusion, the CRS-207 infusion may be delayed to Day 2. CRS-207 administration may be delayed up to 7 days following pembrolizumab administration (if subject is recovering

from an AE); the Sponsor must be notified. If a dose of CRS-207 is delayed beyond 7 days post pembrolizumab, the dose of CRS-207 should be withheld until the next cycle.

[27] **CRS-207** pre-medications include 650 mg of acetaminophen (paracetamol; or maximum permitted by label) administered orally prior to each CRS-207 infusion; a minimum of 0.5 L normal saline administered immediately before CRS-207 infusion and 0.5 - 1 L after infusion is recommended. Additional fluids may be given for persistent tachycardia, fever, or hypotension at Investigator's discretion.

[28] **CRS-207** will be administered at indicated cycles via IV infusion (1×10^9 CFU [starting dose] in sterile saline, USP) over approximately 1 hour; Refer to Pharmacy Manual for preparation and administration requirements). CRS-207 **must not** be administered via central venous catheter or infusion port. IV **must not** have in line filters. Subjects will be observed at least 4 hours after the first CRS-207 infusion and the first cycle with same day dosing. For all subsequent infusions, observe subject at least 2 hours post-infusion. Subjects may be released once they are considered stable; fever alone does not preclude release. Blood samples must not be collected from any central line after infusion of CRS-207 for at least 4 days.

[29] [redacted]

[30] **CRS-207 shedding and clearance** subject subset: samples are collected at select sites only. At Cycles 1 and 2 blood for CRS-207 clearance, urine, rectal swab, and throat swab for CRS-207 shedding will be collected at pre-CRS-207 infusion, and 4 hours (± 30 minutes), 18-24 hours, and 7 days post-CRS-207 infusion. Subjects with samples positive for the presence of CRS-207 will be re-tested until negative testing is confirmed at the direction of the Sponsor. Refer to Laboratory Manual for collection and processing requirements.

ABBREVIATIONS FOR Table 2-1 AND Table 2-2

ALT = alanine aminotransferase; AE = adverse event; AESI = adverse event of special interest; ALC = absolute lymphocyte count; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST=aspartate aminotransferase; CFU = colony-forming units; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; FEV_1 = forced expiratory volume in 1 second; FVC=forced vital capacity; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HLA = human leukocyte antigen; INR = international normalized ratio of prothrombin time; IV = intravenous; MPM = malignant pleural mesothelioma; MRI = magnetic resonance imaging; PBMC = peripheral blood mononuclear cells; PT = prothrombin time; RECIST = Response Evaluation Criteria in Solid Tumors; WBC = white blood cell; WOCBP = woman of childbearing potential.

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
ALC	Absolute lymphocyte count
ANC	Absolute neutrophil count
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BOR	Best overall response
CFR	Code of Federal Regulations
CFU	Colony-forming units
CR	Complete response
CRA	Clinical research associate
CT	Computed tomography
CTCAE	Common Terminology Criteria For Adverse Events
DOR	Duration of response
EAS	Evaluable analysis set
EC	Ethics committee
ECG	Electrocardiogram
ECI	Event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
ELISA	Enzyme-linked immunosorbent assay
EOT	End of Treatment
EU	European Union
FAS	Full analysis set
FDA	United States Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GVAX pancreas	Irradiated, whole-cell, allogeneic tumor immunotherapy
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonisation

Abbreviation	Definition
IHC	Immunohistochemistry
INR	International normalized ratio of prothrombin time
IRB	Institutional Review Board
irRC	immune-related RECIST
IV	Intravenous
LADD	Live, attenuated, double-deleted
Lm	*Listeria monocytogenes*
MedDRA	Medical Dictionary for Regulatory Activities
MHC	Major histocompatibility complex
MPM	Malignant pleural mesothelioma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PD-1	programmed death receptor-1
PD-L1	programmed death receptor ligand-1
pembro	pembrolizumab
PFS	Progression-free survival
PR	Partial response
PT	Prothrombin time
Q3W	Once every 3 weeks
Q6W	Once every 6 weeks
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical Analysis Plan
TCR	T cell receptor
ULN	Upper limit of normal
WBC	White blood cell

5 INTRODUCTION

5.1 Malignant Mesothelioma

Mesothelioma is a life-threatening disease. Of the three primary forms of mesothelioma (pleural, peritoneal, and pericardial), malignant pleural mesothelioma (MPM) is the most common, accounting for 70% of all cases (American Cancer Society, 2014; Ahmed, 2013). MPM is a rare malignancy associated in 90% of cases with exposure to insoluble asbestos fibers that embed in mesothelial cells causing inflammation and scarring (Bridda, 2007; Boffetta, 2007; Carbone, 2012; Robinson, 2005; Spirtas, 1986).

In asbestos-related cases, there is a latency period of 20 to 40 years from first exposure to diagnosis, such that diagnosis often occurs between 50 and 70 years of age (Robinson and Lake, 2005). When symptoms arise, they are frequently mistaken for another condition. As a result, mesothelioma is usually diagnosed in the later stages of its progression, resulting in poor prognosis with a median survival of 10 to 17 months from symptom onset and 9 to 13 months from diagnosis (Spirtas, 1986).

5.1.1 Current Therapies for Malignant Mesothelioma

The best-documented, potentially curative approach to MPM has been surgical MPM resection with the aim for microscopic complete resection. However, the majority of patients present with advanced disease and are therefore not suitable candidates for surgical resection (Robinson and Lake, 2005; Sugarbaker, 1993).

For patients whose disease is unresectable or who otherwise are not candidates for surgery, pemetrexed in combination with cisplatin is standard of care first-line chemotherapy and has been approved by the United States Food and Drug Administration (FDA) and other health authorities for this indication (Rice, 2011). Data from a randomized Phase 3 clinical trial indicated treatment with pemetrexed and cisplatin led to an improvement in overall survival (OS) of 12.1 months compared to 9.3 months with cisplatin alone, with an objective response rate (ORR) of 41% (Hazarika, 2005; Vogelzang, 2003). In a recent randomized Phase 3 clinical study, the addition of bevacizumab to pemetrexed and cisplatin chemotherapy significantly improved OS over pemetrexed and cisplatin alone (median: 18.8 months vs. 16.1 months, respectively; p=0.012). More Grade 3 or 4 events, including proteinuria, hypertension, and arterial thrombotic toxicities were observed in the bevacizumab treatment arm (Zalcman, 2015).

There are no approved therapies for patients in second-line, therefore, new therapies are needed for patients whose disease progresses following first-line chemotherapy. Immunotherapy could improve outcomes by potentiating specific immune responses against tumor antigens. The presence of high levels of $CD8^+$ tumor-infiltrating lymphocytes has associated with better prognosis in subjects undergoing extrapleural pneumonectomy for MPM, supporting the rationale for this approach (Anraku, 2008).

5.2 CRS-207 Immunotherapy

5.2.1 Listeria monocytogenes-Based Immunotherapy

Listeria monocytogenes (*Lm*) is an attractive platform for presentation of tumor-associated antigens and activation of immune response directed against cancer cells. *Lm* provides both a potent stimulation of innate immunity and also induces an adaptive immune response through recruitment and activation of $CD4^+$ and $CD8^+$ T-cells specific for encoded heterologous antigens (Portnoy, 2002; Shen, 1995; Slifka, 1996; Bahjat, 2006).

In wild-type form, *Lm* is a bacterium commonly found in soil and water, and may be present in a variety of raw and processed foods. Listeriosis is a foodborne illness caused by wild-type *Lm* which primarily affects pregnant women and immunocompromised individuals. To address this safety concern a live, attenuated, double-deleted *Lm* (LADD)-based immunotherapy platform was developed (ANZ-100). ANZ-100 has deletions of 2 genes, *actA* and *inlB* (*Lm* Δ*actA*/Δ*inlB*). These genes encode the virulence-determinant proteins ActA and Internalin B, two proteins that facilitate cell-to-cell spread and invasion of nonphagocytic cells, in particular hepatocytes (Brockstedt, 2004). The deletions limit growth in the liver, a principal target organ of infection by wild-type *Lm*, by blocking direct hepatocyte infection via the InlB-hepatocyte growth factor receptor interaction and ActA-mediated cell-to-cell spread into hepatocytes from infected liver-resident Kupffer cells (Portnoy, Auerbuch, Glomski, 2002; Dramsi, 1995). Uptake of ANZ-100 by macrophages and other phagocytic cells in the liver and spleen is retained and results in a local inflammatory response as well as activation and recruitment of natural killer cells and T cells to the liver. In mice, ANZ-100 retains the immunostimulatory potency of wild-type *Lm* but with 1000-fold attenuation of virulence (Brockstedt, 2004). In a Phase 1 dose-escalation study, ANZ-100 doses up to 3×10^8 colony-forming units (CFU) administered by intravenous (IV) infusion in adults with carcinoma and liver metastases were well-tolerated (Le, Brockstedt. 2012).

5.2.2 CRS-207

Mesothelin is a tumor-associated antigen with limited expression on the surface of normal tissues, but highly expressed in many human tumors including virtually all mesothelioma (Hassan, 2004). Mesothelin is more highly expressed in mesotheliomas as compared to other pulmonary carcinomas, with expression by immunohistochemistry (IHC) analysis detected in 75 to 100% of poorly differentiated epithelioid or tubopapillary cases (Miettinen, 2003). These features make mesothelin an attractive target for active tumor-specific immunotherapy.

ANZ-100 was subsequently engineered to express mesothelin, resulting in CRS-207 (*Lm* Δ*actA*/Δ*inlB*/hMeso). CRS-207 contains an expression cassette encoding human mesothelin integrated at the *inlB* locus. After uptake of CRS-207 by dendritic cells and macrophages, mesothelin is expressed and released into the cytosolic compartment and subsequently processed through the endogenous major histocompatibility complex (MHC) Class I presentation pathway, resulting in activation of mesothelin-specific cell-mediated immunity (Le, Brockstedt, 2012).

Other mechanisms to activate mesothelin-specific, cell-mediated immunity may include uptake and cross-presentation of antigens by dendritic cells and other cells after infection by CRS-207 and apoptosis. CRS-207 is a LADD construct rendering it greater than 1000-times less toxic in mice than wild-type *Lm* (Brockstedt, 2004). Nonclinical and clinical data are available and support continued clinical development.

5.2.3 Summary of Nonclinical Studies with CRS-207

A series of nonclinical studies in rodents (mice) and non-human primates (cynomolgus macaques) evaluated the pharmacology, pharmacokinetics (PK) and toxicology of CRS-207. In these studies, CRS 207 elicited mesothelin-specific cellular immunity and therapeutic efficacy in tumor-bearing mice. Repeated-dose safety studies in cynomolgus macaques with CRS-207 and the parent strain, ANZ-100, resulted in an equivalent pro-inflammatory response characterized by transient fluctuations in selected hematological and clinical chemistry parameters and reversible histopathology. Findings of the repeated-dose studies were consistent with a systemic proinflammatory response to a bacterial infection. At the highest dose, CRS 207 was detected in the blood 24 hours after administration, but was undetectable at 72 hours. There were transient and dose dependent decreases in red blood cell, platelet and white blood cell counts. Hepatic and renal function changes were transient and generally less than two-fold from baseline. There were no discernible additive effects of repeat dosing. [redacted]

Overall, nonclinical studies support use of CRS-207 in humans at the proposed dose. A complete summary of nonclinical information for CRS-207 is provided in the Investigator's Brochure (IB).

5.2.4 Summary of Clinical Studies with CRS-207

CRS-207 is being evaluated in multiple clinical studies and multiple oncologic indications. CRS-207, either alone or in combination (sequential or concomitant) with other investigational or approved agents, has been administered to more than 350 subjects with advanced cancers. A complete summary of current clinical information on CRS-207 is provided in the IB.

A Phase 1, first-in-human, multiple-dose, dose-escalation trial (VAC07001) was completed in adults with treatment-refractory MPM, advanced NSCLC, or advanced carcinoma of the ovary or pancreas. The maximum tolerated dose (MTD) was 1×10^9 CFU; CRS-207 was generally well tolerated. While the study enrolled subjects with multiple disease types and was not powered to assess survival, 6/17 subjects (with prior immunotherapy or subsequent radiation) survived at least 15 months after receiving the first dose of CRS-207.

CRS-207 has orphan drug designation for the treatment of MPM in the US and European Union (EU). The clinical development program in MPM currently consists of an open-label Phase 1B study (ADU-CL-02) evaluating CRS-207 (with and without low-dose cyclophosphamide [Cy]) with standard of care chemotherapy (pemetrexed and cisplatin) as a first-line therapy in patients who are not candidates for complete surgical resection. Initial response data from 36 evaluable

patients post-CRS-207 and chemotherapy included 1 (3%) complete response (CR), 20/36 (56%) partial responses (PR) and 13/36 (36%) had stable disease. The interim median progression-free survival (PFS) was 7.6 months (95% CI: 7.1-10.1 months) (Hassan, 2016).

Treatment emergent adverse events (TEAEs) temporally related to CRS-207 administration which are common and may vary in degree of severity include fevers, chills, nausea, vomiting, fatigue, headache, and hypotension. Changes in hepatic enzyme levels and hematological parameters (lymphopenia) are also anticipated to varying degrees of severity. These effects are likely a consequence of the mechanism of action of CRS-207 through the activation of the innate immune system and release of proinflammatory cytokines and chemokines. Some of these infusion-related events may be mitigated by pre-medication with acetaminophen and administration of saline prior to and following CRS-207 infusion. Based on available results from clinical studies, continued clinical development of CRS-207 is warranted.

5.3 Rationale for CRS-207 and Pembrolizumab Immunotherapy in Malignant Pleural Mesothelioma

For patients with unresectable MPM or who otherwise are not candidates for surgery, pemetrexed and cisplatin is the standard of care as first-line chemotherapy but confers limited benefit. There is an unmet medical need for patients who have disease progression following at least one systemic chemotherapy regimen.

The programmed death receptor-1 (PD-1) is a checkpoint protein on T cells that normally inhibits T cells from attacking other cells in the body. Overexpression of the programmed death receptor ligand-1 (PD-L1) on cancer cells further evades immune attack by T cells. PD-L1 is overexpressed in MPM and associated with poor prognosis (Alley, 2015). Checkpoint inhibitors, including antibodies targeting PD-1, block the PD-1/PD-L1 interaction and boost the immune response against cancer cells. Monoclonal antibodies targeting PD-1 include pembrolizumab (Merck, 2014) and nivolumab have been approved for use in multiple tumor types and are currently being studied in several additional indications including MPM.

Initial results from studies with monoclonal antibodies targeting PD-1 have shown evidence of clinical benefit in subjects with previously-treated MPM. Preliminary results from a Phase 1B trial (KEYNOTE-028) of pembrolizumab in 25 subjects with PD-L1-positive MPM (80% with prior chemotherapy) showed a 24% ORR and 76% DCR. AEs related to pembrolizumab occurred in 15 subjects (60%); drug-related events in > 25% of subjects were nausea, fatigue, and decreased appetite. No deaths or discontinuations were attributable to treatment; 3 subjects (12%) had grade ≥3 AEs related to treatment (Alley, 2015). Interim analysis from a Phase 2 trial (NivoMes) of nivolumab in 18 subjects with previously-treated MPM showed 39% DCR and 28% ORR (Quispel-Janssen, 2016).

The addition of a checkpoint inhibitor to CRS-207 may enhance the immunotherapeutic potential of these agents by enabling stimulation of targeted immune responses to specific tumor antigens.

[redacted]

Initial data from an ongoing clinical study of CRS-207 with agents targeting the PD1 blockade (i.e. nivolumab) suggests an acceptable tolerability profile.

The current study is designed to evaluate whether CRS-207 with pembrolizumab effectively primes specific immune responses and results in clinical benefit for patients with MPM who failed prior therapy. It is hypothesized the expansion of tumor-specific T cells in context of blocking the PD-1/PD-L1 pathway may ultimately provide enhanced anti-tumor efficacy. Although there are no precedent data on the safety of CRS-207 and pembrolizumab combination, CRS-207 is currently being evaluated with the PD-1 inhibitor nivolumab in an investigator-sponsored Phase 2 study (ADU-CL-06; NCT02243371). The study is evaluating survival, safety and immune response following treatment with CRS-207/GVAX pancreas/Cy with or without nivolumab in subjects with previously-treated pancreatic cancer. Initial data from this ongoing clinical study suggests an acceptable tolerability profile of both agents at full dose (CRS-207 1×10^9 CFU with nivolumab at 3 mg/kg). Refer to the Investigator's Brochure for additional information. These data suggest that a dose escalation Phase 1 component in the current study is not required.

5.3.1 CRS-207 Dose Selection Rationale

CRS-207 has been shown to be well-tolerated at the proposed route of administration and dose for this study (Le, Dubenksy, 2012). The dose of CRS-207 was chosen based on the Phase 1, dose-escalation study (VAC07001) in which 1×10^9 CFU was determined to be the MTD and shown to be well-tolerated in patients with advanced cancer (including MPM) and induced a mesothelin-specific immune response. The 1×10^9 CFU dose level was also used in the Phase 1B trial (ADU-CL-02) in MPM where initial analysis demonstrates clinical response and acceptable tolerability (Hassan, 2015). CRS-207 dosing at 1×10^9 CFU has been associated with mostly limited and transient infusion-related reactions including fevers, chills, nausea, vomiting, fatigue, headache, and hypotension, and changes in hepatic enzyme levels and hematological parameters (lymphocyte counts).

The initial CRS-207 dosing regimen (once every 3 weeks; Q3W) in this study was designed to synergize with pembrolizumab to optimally prime an immune response. If subjects are clinically stable and/or responding to treatment, CRS-207 infusions will continue Q6W to sustain the immune response. In other clinical studies, CRS-207 has been administered every 2 to 8 weeks.

5.3.2 Pembrolizumab Dose Selection Rationale

[redacted]

6 STUDY OBJECTIVES

The objectives of the study are to:

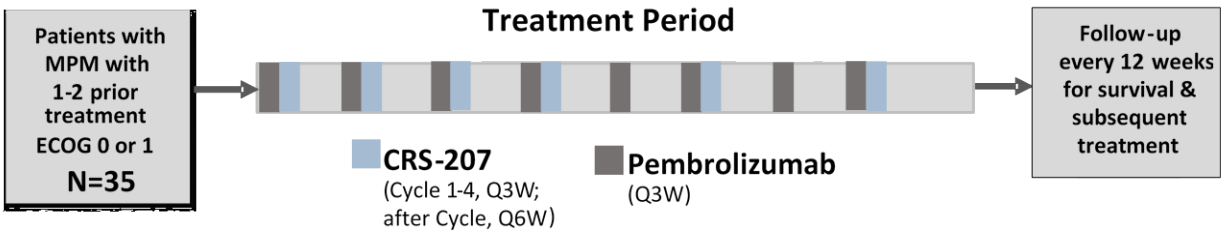
- Assess safety and tolerability of CRS-207 and pembrolizumab (Merck, 2014)
- Evaluate the effect of CRS-207 and pembrolizumab on tumor response, pulmonary function, and survival
- Characterize the immune response following administration of CRS-207 and pembrolizumab

7 INVESTIGATIONAL PLAN

7.1 Study Design and Duration

ADU-CL-13 is a single-arm, open-label, multicenter Phase 2 study to evaluate the safety and efficacy of CRS-207 administered with pembrolizumab (Merck, 2014). The population for this study will consist of approximately 35 adults with histologically-confirmed MPM (epithelial or biphasic) whose disease has progressed after prior systemic chemotherapy. The study will consist of a Screening Period, Treatment Period (including a Safety Run-in), and a Follow-up Period (Figure 7.1).

Figure 7.1 ADU-CL-13 Study Schema



ECOG = Eastern Cooperative Oncology Group; MPM = malignant pleural mesothelioma; Q*x*W = every x weeks

CRS-207 and pembrolizumab will be administered in 3-week cycles. For Cycle 1, pembrolizumab (200 mg) will be administered by intravenous infusion (IV) over 30 minutes on Day 1 and CRS-207 (starting dose 1×10^9 colony-forming units [CFU]) will be administered IV over 1 hour on Day 2. If the infusions are well tolerated, pembrolizumab and CRS-207 may be administered on the same day (Day 1) for subsequent cycles. After 4 cycles, pembrolizumab will continue to be administered on Day 1 at each treatment cycle (every 3 weeks; Q3W); CRS-207 will be administered once every 6 weeks (i.e. every other treatment cycle; Q6W). Alternatively, study drug administration may revert back to consecutive day-dosing regimen as performed in Cycle 1 (Day 1 pembrolizumab and Day 2 CRS-207). Treatment cycles with pembrolizumab will continue for up to 35 cycles as long as there is adequate safety and potential for clinical benefit. After cycle 35, subjects may receive CRS-207 monotherapy if subject meets dosing eligibility, is clinically stable, and the subject is deriving clinical benefit. If radiographic disease progression is observed, clinically stable subjects who meet dosing eligibility may continue to receive CRS-207 and pembrolizumab at the discretion of the Investigator. Subjects who experience unacceptable toxicity(ies) related to CRS-207 or pembrolizumab may continue on study and receive CRS-207 or pembrolizumab monotherapy with approval from Medical Monitor. Subjects who experience unacceptable toxicity(ies) related to both CRS-207 and pembrolizumab in Cycle 1 should be discontinued from the treatment. However, if in the opinion of the investigator, the subject is deriving clinical benefit from the study treatment, the subject may be allowed to continue with treatment after discussion with the Medical Monitor.

A Safety Run-in will be completed since there are no precedent data on the use of pembrolizumab with CRS-207. Treatment of the first 6 subjects will be staggered, with no more than 1 subject treated per week; subjects will be monitored for safety during the first 28 days (at least through 7 days after the Cycle 2 dose). During the Safety Run-in, evaluable subjects are defined as those who remain on study for the 28-day monitoring period, subjects with unacceptable toxicity, and subjects who are discontinued for safety reasons at the Investigator's discretion (even if criteria for unacceptable criteria are not met). In the event 2 subjects in the first 6 treated experience unacceptable toxicity(ies), the Safety Review Team will be convened to determine if the dose of CRS-207 will be reduced in subsequently enrolled subjects in half-log increments.

Safety data including all unacceptable toxicities will be reviewed by a Safety Review Team comprised of participating investigators in the study, the Medical Monitor, and representatives of the Sponsor. Once the Safety Run-in is complete, safety will continue to be evaluated on an ongoing basis in this open-label study. Cumulative clinical experience with CRS-207 and pembrolizumab will be used to assess whether adverse events (AEs) are considered expected. If >33% of subjects dosed experience unacceptable toxicities attributable to study drug(s), the Safety Review Team will be convened to determine if dosing will be suspended.

The schedule of events is provided in Table 2-1 or Table 2-2 for subjects who experience tolerability issues and continue to follow the consecutive-day dosing regimen). Tumor imaging and pulmonary function will be assessed at baseline (Screening) and during the Treatment Period approximately every 6 weeks starting at Cycle 3. Tumor measurement and assignment of response will be determined by local Investigators using the modified response evaluation criteria in solid tumors (modified RECIST) for MPM (Byrne and Nowak, 2004). If radiographic disease progression is observed, another scan should be done at least four weeks later to confirm disease progression prior to treatment discontinuation. Peripheral blood will be collected to assess immune responses directed against *L. monocytogenes*, mesothelin, and other tumor-associated antigens. Paired tumor biopsies will be collected at Screening and during Cycle 2 to explore the association of programmed death receptor ligand-1 (PD-L1) expression and tumor-infiltrating lymphocyte characteristics with clinical responses.

The Treatment Period is defined as the time from the first dose of study drug administration until discontinuation of both CRS-207 and pembrolizumab, and completion of an End of Treatment (EOT) visit. All subjects must complete an End of Treatment (EOT) visit no more than four weeks following the final dose of study drug and/or prior to receipt of other cancer-related treatment. Subjects will be administered antibiotics at the EOT visit to eliminate any potentially residual CRS-207 (refer to Section 7.3.6.1).

At the end of the Treatment Period, subjects will enter the Follow-up Period of the study and will be followed for survival and subsequent cancer-related therapies every 3 months until death or close of study by the Sponsor. Sites will attempt to obtain vital status data from public records or

other external sources where possible if a subject withdraws consent from study (i.e. refuse follow-up for vital status) or is documented as lost to follow up.

7.1.1 Discussion of Study Design

The study was designed as a single-arm, open-label, multicenter Phase 2 study. The study is intended to provide the maximum amount of information regarding CRS-207 and pembrolizumab safety and tolerability, along with indicators of clinical efficacy and overall survival. Paired tumor biopsies and blood samples will provide an initial investigation into the mechanism of action of this regimen.

There are currently no approved therapies beyond first-line treatment of MPM. Given the life-threatening nature of the disease, a placebo-controlled trial is not appropriate in this setting. Since all subjects will receive the same investigational products, randomization and blinding are unnecessary; study drug will be provided open-label. The study is being conducted as a single-arm trial to evaluate initial safety and efficacy signals before initiating a larger randomized trial.

For the first cycle, pembrolizumab and CRS-207 will be dosed on consecutive days (pembrolizumab on Day 1 and CRS-207 on Day 2). If Cycle 1 is well tolerated, dosing of both agents will occur on the same day (Day 1) for subsequent cycles. Based on prior clinical experience and expected infusion reactions, it is anticipated that the same-day regimen will be tolerated and more convenient for patients. A Safety Run-in is planned to monitor safety for the first 6 subjects.

The sample size is intended to explore whether the proportion responding to CRS-207 and pembrolizumab is similar to or better than what is expected based on data from other clinical studies with checkpoint inhibitors in subjects with MPM. The estimate of ORR used for sample size determination is based on a review of published literature, where Investigator-assessed response rates from 24% (Alley, 2015) to 28% (Quispel-Janssen, 2016) were reported in studies of patients with MPM. Since these studies included all histological subtypes (sarcomatoid, epithelial and biphasic) and some studies required confirmation of PD-L1 expression prior to treatment, there is no direct published historical comparison in a similar population as intended for this study, however due to the lower expression of PD-L1 in the epithelial subtype (Cedrés, 2015), observed response rates may be lower than the published studies.

7.2 Study Population

The population for this study will consist of approximately 35 adults with histologically-confirmed MPM (epithelial or biphasic with < 50% sarcomatoid) whose disease has progressed following at least one prior systemic chemotherapy regimen for advanced disease. Prior treatment must have included pemetrexed (or anti-folate) in combination with a platinum agent since this is approved therapy for MPM and recognized as standard of care in clinical practice. Individuals with immunosuppressive disorders or who require immunosuppressive medications will be excluded. An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

and serum albumin levels serve as prognostic indicators of participants more likely to benefit from treatment.

7.2.1 Inclusion Criteria

Individuals eligible to participate in this study must meet all of the following criteria:

1. Histologically-confirmed epithelial or biphasic MPM; biphasic tumors must have a predominantly (≥50%) epithelial component
2. No more than 2 prior lines of anti-cancer therapy, one of which must have included pemetrexed and a platinum. Documented radiographic progression of disease after treatment with pemetrexed and a platinum is required.
3. Measurable disease as defined by modified RECIST for MPM
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
5. Adequate organ and marrow function at Screening, as defined by:
   - White blood cell count ≥ 3000/ µL
   - Absolute neutrophil count ≥ 1500/µL
   - Absolute lymphocyte count ≥ 800/µL
   - Platelet count ≥ 100,000/µL
   - Bilirubin ≤ 1.5 × institutional upper limit of normal (ULN), or ≤ 3 × institutional ULN if due to Gilbert's disease
   - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × institutional ULN or ≤ 5 × ULN for subjects with liver metastases
   - Albumin ≥ 3.0 g/dL
   - Serum creatinine ≤1.5 × institutional ULN
   - Hemoglobin ≥ 9.0 g/dL
   - International normalized ratio (INR) or prothrombin time (PT) ≤1.5 × ULN and activated partial thromboplastin time (aPTT) ≤1.5 × ULN (if receiving anticoagulant therapy, values should be within therapeutic range of intended use)

   Any Grade 3 or higher abnormality in any serum chemistry or hematology parameter must be discussed and approved by the Medical Monitor prior to enrollment (even if considered not clinically significant)
6. Aged 18 years and over
7. Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) ≥ 45% of predicted value as measured by spirometry; and oxygen saturation ≥ 90% on room air as measured by pulse oximeter
8. Women of childbearing potential (WOCBP) and fertile males with WOCBP partners must use highly effective contraception [per (CTFG, 2014)] throughout the Treatment Period

(from first dose and through 120 days after final dose of study drug). Contraception must include at least one barrier method to minimize risk of fluid transmission.

9. Provide written informed consent and is willing and able to comply with all study procedures.

7.2.2 Exclusion Criteria

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

1. Pleurodesis within 14 days prior to first dose of study drug
2. Has a diagnosis of immunodeficiency, receiving TNF pathway inhibitors, PI3 kinase inhibitors, chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug
3. Active second malignancy with the exception of any of the following:
   - Adequately treated basal cell carcinoma
   - Squamous cell carcinoma of the skin, or *in situ* cervical cancer
   - Low-risk prostate cancer (i.e. Gleason score < 7 and prostate specific antigen < 10 ng/mL); or
   - Any other cancer from which the individual has been disease-free for ≥ 3 years
4. Untreated or unstable brain metastases. Individuals with treated (surgically excised or irradiated) and stable brain metastases are eligible as long as the subject has adequately recovered from treatment and the treatment was ≥ 28 days prior to first dose of study drug. A baseline brain computed tomography (CT) with contrast or magnetic resonance imaging (MRI) within 14 days prior to first dose of study drug must be negative for new brain metastases.
5. Prior anti-cancer monoclonal antibody within 4 weeks prior to first dose of study drug, or not recovered from adverse effects due to agents administered more than 4 weeks earlier
6. Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to first dose of study drug
7. Ongoing adverse effects (i.e. ≤ Grade 1 or at baseline) due to a previously administered anti-cancer agent. Individuals with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion
8. History of (non-infectious) pneumonitis that required steroids or current pneumonitis
9. History of interstitial lung disease
10. Received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including G-CSF, GM-CSF or recombinant erythropoetin) within 4 weeks prior to first study drug administration
11. Active infection requiring systemic therapy

12. Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent, or agents targeting other checkpoint pathways (e.g. CTLA-4)
13. Prior immunotherapy with CRS-207 or any other *Listeria*-based agent, therapeutic cancer vaccine, or adoptive T cell immunotherapy
14. Received any prophylactic vaccine within 14 days of first dose of study drug or received a live vaccine within 30 days of planned start of study therapy. Seasonal flu vaccines that do not contain live virus are permitted.
15. Participated in any other study in which receipt of an investigational new drug, or investigational device occurred within 28 days of first dose of study drug
16. Clinically significant heart disease (such as uncontrolled angina, myocardial infarction within 3 months of study initiation, congestive heart failure, or New York Heart Association Class III or IV heart failure)
17. Know valvular heart disease that requires antibiotic prophylaxis for prevention of endocarditis
18. Known allergy to <u>both</u> penicillin and sulfa drugs
19. Known or suspected allergy or hypersensitivity to yeast or any other component of CRS-207 (e.g. glycerol) or pembrolizumab; or history of severe hypersensitivity (≥ Grade 3) to pembrolizumab and/or any of its excipients.
20. History of autoimmune disease that has required systemic treatment in the past 2 years, including:
    - Inflammatory bowel disease (including ulcerative colitis and Crohn's Disease)
    - Rheumatoid arthritis
    - Systemic progressive sclerosis (scleroderma)
    - Systemic lupus erythematosus
    - Autoimmune vasculitis (e.g. Wegener's granulomatosis)
    - Central nervous system or motor neuropathy considered of autoimmune origin (e.g. Guillain-Barré syndrome, myasthenia gravis, multiple sclerosis)

    Individuals with vitiligo, moderate to severe psoriasis, Sjogren's Syndrome, interstitial cystitis, Graves' or Hashimoto's Disease, celiac disease, diabetes mellitus type 1, or hypothyroidism stable on hormone replacement will be allowed with Medical Monitor approval.
21. Received a diagnosis of human immunodeficiency virus (HIV)
22. Received a diagnosis of hepatitis B, or hepatitis C for which there is no clear evidence of natural immunity, immunity subsequent to vaccination, or successful eradication of the virus following antiviral therapy (individuals who are hepatitis C antibody positive may be enrolled if negative viral load confirmed at Screening)
23. If WOCBP, pregnant or breastfeeding; negative pregnancy status must be confirmed within 24 hours of first dose of study drug

24. Implanted medical devices that pose high risks for colonization and cannot be easily removed (e.g., artificial heart valves, pacemakers, prosthetic joints, orthopedic screw(s), metal plate(s)) if infection occurs. Other common devices such as venous access devices (e.g., Port-a-Cath or Mediport) may be permitted as well as arterial and venous stents and dental and breast implants that were placed more than 3 months prior to first dose of study drug
25. Major surgery or significant traumatic injury occurring within 28 days prior to first dose of study drug. If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
26. Unhealed wound or ulcer; or a bone fracture considered non-healing
27. History or evidence of inherited bleeding diathesis or coagulopathy
28. Unable or unwilling to withhold or discontinue any prohibited or restricted medications/procedures for the specified periods during the study
29. Intercurrent illness that is either life-threatening or of clinical significance such that it might limit compliance with study requirements, or in the Investigator's assessment would place the subject at an unacceptable risk for study participation

7.2.3 Dosing Eligibility and Delayed Dosing

Subjects must have adequate organ function confirmed (as defined by the laboratory values in Table 7-1 prior to each dosing cycle where CRS-207 is administered; laboratory tests may be performed up to 3 days before dosing.

Table 7-1. Dosing-Eligibility Requirements

Hematologic	Renal	Hepatic
WBC ≥ 3000/μL ANC ≥ 1000/μL Platelets ≥ 90,000/μL Hemoglobin ≥ 8 g/dL	Creatinine ≤ 1.5 × ULN	AST/ALT ≤ 5× ULN Bilirubin ≤ 1.5× ULN OR ≤ 3 × ULN if due to Gilbert's disease
ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = institutional upper limit of normal; WBC = white blood cell		

Subjects who do not meet dosing eligibility requirements will be monitored; dosing may be delayed up to 2 weeks, after which time it will be considered missed and the subject would continue onto the next scheduled dose. If a dose is delayed more than 2 weeks, contact the Medical Monitor for further instruction on continued dosing.

Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (refer also to Section 7.3.5.1). If subjects on same-day dosing schedule experience severe infusion-related reactions related to the pembrolizumab infusion, the CRS-207 infusion may be delayed to Day 2. If the subject experiences a new AE or is recovering from an AE, CRS-207 administration may be delayed up to 7 days following pembrolizumab administration; the Sponsor must be notified. If a dose of CRS-207 is delayed beyond 7 days post pembrolizumab, the dose of CRS-207 should be withheld until the next cycle.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g. elective surgery, unrelated medical events, vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the Subject's study record.

7.2.4 Subject Discontinuation

Subjects will be encouraged to complete the study; however, they may voluntarily withdraw from treatment or the study at any time. The Investigator will provide a written explanation describing the reason for discontinuation from treatment or study in a source document, which will be entered into the electronic case report form (eCRF). Subjects who wish to discontinue treatment will be encouraged to complete the planned administration of antibiotics, complete EOT assessments, post-treatment monitoring for CRS-207, and participate in the Follow-up Period. In the case of subjects lost to follow-up, attempts to contact the subject must be made and documented in the subject's study records. Sites will attempt to obtain vital status data from public records or other external sources where possible if a subject withdraws consent from study (i.e. refuse follow-up for vital status) or is lost to follow up.

A subject in this clinical study may be discontinued from treatment for any of the following reasons:

- The subject withdraws consent or requests discontinuation for any reason
- Occurrence of any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the subject
- Pregnancy
- Subject failure to comply with protocol requirements or study-related procedures
- Termination of the study by the Sponsor or the regulatory authority

Subjects who experience unacceptable toxicity(ies) related to CRS-207 or pembrolizumab may continue on study and receive CRS-207 or pembrolizumab monotherapy. Subjects who experience unacceptable toxicity(ies) related to both CRS-207 and pembrolizumab in Cycle 1 should be discontinued from the treatment. However, if in the opinion of the investigator, the subject is deriving clinical benefit from the study treatment, the subject may be allowed to continue with treatment after discussion with the Medical Monitor. Alternatively, study drug administration may revert back to consecutive day-dosing regimen as performed in Cycle 1. If subjects experience unacceptable toxicity(ies) related to both CRS-207 and pembrolizumab that is ≥ Grade 3, treatment should be discontinued and Medical Monitor notified.

7.2.4.1 Stopping Rules

There are no formal stopping rules for this study. Once the Safety Run-in Period is complete, safety will continue to be evaluated on an ongoing basis in this open-label study. Cumulative clinical experience with CRS-207 and pembrolizumab will be used to assess whether AEs are considered expected. If >33% of subjects dosed experience unacceptable toxicities attributable to study drug(s), the Safety Review Team will be convened to determine if dosing will be suspended.

7.3 Study Treatments and Additional Medications

Subjects will receive the assigned treatment course described in Table 7-2.

Table 7-2 ADU-CL-13 Study Treatment Course

Study Drug	Dose / Route	Treatment Course
Pembrolizumab	200 mg administered IV over 30 min (-5 min/+10 min)	Day 1 of each cycle
CRS-207	1×10^9 CFU administered IV over ~ 1 hour	Day 2 of Cycle 1 Day 1 of Cycle 2, 3, 4; Q6W thereafter [1]

CFU = colony-forming unit; IV = intravenous; Q6W = every 6 weeks

[1] Subjects who experience tolerability issues may continue to follow the consecutive-day dosing regimen as in Cycle 1 and follow the Schedule of Events for Consecutive Day Dosing (Table 2-2).

7.3.1 Safety Run-In Period

A Safety Run-in will be completed since there are no precedent data on the use of pembrolizumab with CRS-207. Treatment of the first 6 subjects will be staggered, with no more than 1 subject treated per week. Subjects will be monitored for unacceptable toxicities during the Safety Run-in Period [the first 28 days (through 7 days after the Cycle 2 dose)]. During the Safety Run-in evaluable subjects are defined as those who remain on study for the 28-day monitoring period, subjects with unacceptable toxicity, and subjects who are discontinued for safety reasons at the Investigator's discretion (even if criteria for unacceptable criteria are not met). In the event 2 subjects in up to 6 experience unacceptable toxicity(ies) during the Safety Run-in Period, the Safety Review Team will be convened to determine if subsequent subjects enrolled will be administered CRS-207 at a dose reduced by a half-log (dose level -1). In the event of 2 subjects in up to the next 6 subjects treated experience unacceptable toxicity(ies), the Safety Review Team will reconvene to determine if the dose for CRS-207 will be further reduced by a half-log (dose level -2) for the remaining subjects to be enrolled. The medical monitor, participating investigators, and Sponsor may request that the Safety Review Team convene at any time during the Safety Run-in Period to review and evaluate available safety data. The dose levels and dose reduction permutations are provided in Table 7-3.

Table 7-3 Safety Run-in Dose Levels and Dose Reduction

Dose level	Pembrolizumab	CRS-207
1	200 mg	1×10^9 CFU
-1	200 mg	3×10^8 CFU
-2	200 mg	1×10^8 CFU

Subjects who experience unacceptable toxicity(ies) related to CRS-207 or pembrolizumab may continue on study and receive CRS-207 or pembrolizumab monotherapy with approval from Medical Monitor.

7.3.1.1 Unacceptable Toxicity Criteria

The unacceptable toxicity criteria will be any of the following unless clearly related to an alternative cause other than study drug:

- Grade 5 toxicity
- Grade 4 non-hematologic toxicity (not laboratory)
- Grade 4 hematologic toxicity lasting ≥7 days
- Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care
- Any Grade 3 or Grade 4 non-hematologic laboratory value if:
    - Medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week
- Grade 3 or 4 febrile neutropenia
    - Grade 3 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour
    - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 °C (101 °F) or a sustained temperature of ≥38 °C (100.4 °F) for more than one hour, with life-threatening consequences and urgent intervention indicated
- Thrombocytopenia <25,000/mm^3 if associated with:
    - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
    - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit
- Delay of >8 days starting Cycle 2 due to study drug-related toxicity
- Administration of systemic steroids to treat an immune-mediated reaction
- Serum chemistry laboratory values consistent with Hy's Law criteria (i.e. all 3 of the following must coexist):
    - ALT or AST ≥ 3 × ULN
    - Total bilirubin ≥ 2 × ULN

- ALP < 2 × ULN

Safety data and all unacceptable toxicities will be reviewed by the Safety Review Team comprised of participating investigators in the study, the Medical Monitor, and Sponsor representatives. Once the Safety Run-in is complete, safety will continue to be evaluated on an ongoing basis in this open-label study. Cumulative clinical experience with CRS-207 and pembrolizumab will be used to assess whether AEs are considered expected.

Subjects who experience an unacceptable toxicity related to CRS-207 or pembrolizumab may continue on study and receive either pembrolizumab or CRS-207 monotherapy with approval by the Medical Monitor.

7.3.1.2 Safety Monitoring

Safety data including all unacceptable toxicities will be reviewed by a Safety Review Team comprised of participating investigators in the study, the Medical Monitor, and Sponsor representatives. Following the safety run-in period, safety will continue to be evaluated on an ongoing basis. If >33% of subjects dosed experience unacceptable toxicities attributable to study drug(s), the Safety Review Team will be convened to determine if dosing will be suspended. Cumulative clinical experience with CRS-207 and pembrolizumab will be used to assess whether AEs are considered expected.

Subjects who experience unacceptable toxicity(ies) related to CRS-207 or pembrolizumab may continue on study and receive CRS-207 or pembrolizumab monotherapy with approval from Medical Monitor. Subjects who experience unacceptable toxicity(ies) related to both CRS-207 and pembrolizumab in Cycle 1 should be discontinued from treatment. However, if in the opinion of the investigator, the subject is deriving clinical benefit from the study treatment, the subject may be allowed to continue with treatment after discussion with the Medical Monitor.

7.3.2 Method of Assigning Subjects to Treatment

All subjects will be sequentially assigned a unique subject identification number upon providing informed consent. The study is designed as a single-arm study; all subjects will receive CRS-207 and pembrolizumab as indicated.

7.3.3 Blinding

ADU-CL-13 is a single-arm, open-label study. Due to the expected infusion-related reactions and required pre-medications associated with CRS-207 administration, it is not feasible or necessary to conduct the study under blinded conditions. All study treatments will be administered open-label; no study participants or site personnel will be blinded to study treatment.

7.3.4 Investigational Product: CRS-207

CRS-207 is a LADD strain derived by deletion of *actA* and *inlB* coding sequences from a streptomycin-resistant, wild-type strain and insertion of the *hMeso* coding sequence. The CRS-

207 drug product is formulated as 1×10^9 CFU suspended in [redacted], filled into a single-use 2-mL glass vial with a gray butyl stopper and aluminum crimp seal with a flip-off cap. CRS-207 is stored frozen at -60 ºC or colder until just before IV administration. CRS-207 is supplied by the Sponsor. Additional information on CRS-207 may be found in the Pharmacy Manual and IB.

7.3.4.1 Biosafety and Environmental Precautions

In wild-type form, *Lm* is a bacterium commonly found in soil and water, and may be present in a variety of raw and processed foods. Listeriosis is a foodborne illness caused by wild-type *Lm* which primarily affects pregnant women and immunocompromised individuals. Direct human-to-human spread of *Lm* is believed to be limited mainly to vertical transmission from mother to neonate. CRS-207 is a LADD construct originating from wild-type *Lm* which contains deletions of 2 virulence genes that render it greater than 1000-times less toxic than wild-type *Lm* in mice (Brockstedt, 2004).

LADD-based immunotherapies (*Lm* Δ*actA*/Δ*inlB*) including CRS-207, have been designated as Risk Group 1 by the Aduro Institutional Biosafety Committee. Risk Group 1 is consistent with the guidance by the German ZKBS (Central Commission for Biological Safety) for classification of *Lm* strains with deletion in genes *prFA, hly, actA*, and *plcB* (1999). Individuals who prepare CRS-207 for infusion must take appropriate precautions (e.g. gloves, laboratory coat, face protection, needle stick or sharps precautions) to avoid contamination or direct contact with the agent. Once prepared for infusion, the chance for direct exposure to CRS-207 by study personnel should be greatly diminished. However, study personnel and staff should continue to adhere to the institutional guidelines for standard precautions.

Based on nonclinical studies and available clearance and shedding data from clinical studies, a subject who receives CRS-207 is unlikely to spread an infection to others. Subjects receiving CRS-207 should be counseled to minimize the potential risk of spreading CRS-207 by practicing good health hygiene (e.g. hand-washing) as with any potential infectious agent, and adhering to protocol requirements for barrier method of contraception during sexual intercourse.

7.3.4.2 CRS-207 Administration

CRS-207 is intended for IV administration (IV must not have in line filters). The intended dose of CRS-207 is 1×10^9 CFU diluted in sterile saline and administered by IV infusion. Additional details for storage and preparation of CRS-207 are provided in the study Pharmacy Manual.

Use of Central Lines

To avoid contamination of a central line (e.g. infusion ports, peripherally inserted central catheter) with CRS-207 during and after infusion:

- CRS-207 must **NOT** be administered through a central line or infusion ports

- Central lines must **NOT** be used or accessed for any reason once CRS-207 infusion has been initiated (including blood draws, medication administration or line flushing; blood draws prior to infusion through a port or central line are allowed) and through 4 days after infusion
- Central lines must be clearly labeled with tape or other method indicating date when port may be used again after CRS-207 infusion

Pre-Medication and Post-Infusion Observation

Before each CRS-207 infusion, subjects should be pre-medicated with 650 mg (or maximum dose permitted by label) acetaminophen (paracetamol). Adequate hydration is important to mitigate infusion-related reactions. All subjects are required to receive a minimum of 0.5 L of normal saline immediately before CRS-207 infusion; an additional 0.5 - 1 L after infusion is recommended, as tolerated. Additional fluids may be given for persistent tachycardia, fever, or hypotension based on Investigator's discretion.

Subjects will be observed in the clinic for at least 4 hours after the first CRS-207 infusion and first cycle with same day dosing; and at least 2 hours following each subsequent infusion. Subjects should continue to be monitored after infusion and released once they are considered clinically stable. Vital signs will be monitored (Section 7.4.3.1). Presence of fever alone in the absence of other clinical signs and symptoms does not preclude the subject from being released. Hospital admissions for overnight monitoring will not be considered an SAE unless the event meets criteria for seriousness other than hospitalization.

During and after CRS-207 infusions, subjects may experience fever, chills/rigor, blood pressure changes, nausea, and vomiting. Refer to Section 7.3.7 and the IB for additional details on CRS-207 administration and supportive care.

7.3.4.3 CRS-207 Dose Modification

CRS-207 at the proposed dose level has been well tolerated and dose reductions are not anticipated. The dose of CRS-207 may be reduced outside of the Safety Run-in period as recommended by the Safety Review Team. However, in the event of AEs of concern that are attributable to CRS-207 the Medical Monitor should be contacted.

7.3.5 Investigational Product: Pembrolizumab

Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa. Pembrolizumab is not currently approved for treatment of MPM and is being used as an investigational agent in this study. However, the approved package insert should be consulted for additional product information on storage, preparation and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions.

Pembrolizumab for injection is a sterile, preservative-free, clear to slightly opalescent, colorless to slightly yellow solution that requires dilution for IV infusion. Each vial contains 100 mg of pembrolizumab in 4 mL of solution. Each 1 mL of solution contains 25 mg of pembrolizumab and is formulated in: L-histidine (1.55 mg), polysorbate 80 (0.2 mg), sucrose (70 mg), and Water for Injection, USP.

7.3.5.1 Pembrolizumab Administration

Pembrolizumab will be diluted and administered as a dose of 200 mg using a 30-minute IV infusion. Sites should target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps, a window between -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes -5 min/+10 min). Do not co-administer other drugs through the same infusion line. Vital signs (blood pressure, pulse, respiratory rate, temperature) will be measured pre- and post-infusion.

Pembrolizumab infusions will be administered Q3W for up to 35 cycles. The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion and administration of infusion solution.

7.3.5.2 Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 7-4.

Table 7-4 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (i.e. diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e. peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue1		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g. propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue1		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g. levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.
2. For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

7.3.6 Antibiotics

To eliminate any potentially residual CRS-207, subjects will be administered antibiotics at the EOT visit and prior to receiving subsequent cancer-related therapy. [redacted]

Consult the package inserts for amoxicillin, trimethoprim, and sulfamethoxazole for product information on dosage and administration, contraindications, warnings/precautions, adverse reactions, and drug interactions.

[redacted]

7.3.7 Concomitant Medications and Procedures

Subjects may receive concomitant medications as required, unless specifically restricted or prohibited in this study (Section 7.3.8). Minor procedures such as dental work, skin biopsy, celiac plexus block, biliary stents, mediport/port insertion, and video-assisted thoracic surgery biopsy are allowed; however, CRS-207 should not be administered within 14 days of the procedure or until the investigator determines there is no additional risk to the subject.

During the course of the study, subjects are anticipated to continue the use of prescribed medications identified during the screening procedures, consistent with study inclusion and exclusion criteria.

Concomitant medications used in this study include:

- Acetaminophen (paracetamol) prior to each CRS-207 infusion
- Antiemetics according to American Society for Clinical Oncology guidelines (Basch, 2011)
- Antipyretics to treat fever or to prevent recurrence of fever post-CRS-207 infusion
- IV narcotics such as morphine or meperidine (per institutional policy) for rigors associated with CRS-207 dosing
- [redacted]

7.3.8 Prohibited Medications and Procedures

A subject may be removed from the study for use of prohibited medications or procedures. Approval must be obtained from the Medical Monitor for a subject to continue dosing if a prohibited medication is administered within the specified timeframes. The following therapies are not permitted or restricted during the study:

- Non-study chemotherapy or immunotherapy (approved or investigational)
- TNF pathway inhibitors or PI3 kinase inhibitors
- Palliative radiation
- Live vaccines (examples of live vaccines include, but are not limited to: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid [oral] vaccine). Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Any major surgery or surgical procedure; if required must be discussed with the Medical Monitor to determine if it is appropriate for the subject to continue study treatment
- Any other investigational product

If a subject requires an emergent implant of a prohibited device while on therapy, the subject will receive a 14-day IV antibiotic regimen (see Section 7.3.6.1).

In addition, the following medications are only restricted prior to and after CRS-207 infusions as indicated:

- Systemically active steroids for more than 3 days or use of any systemic steroids within 14 days before or after CRS-207 infusion, with the exception of inhaled steroids
- Filgrastim (granulocyte colony stimulating factor; G-CSF) or sargramostim (granulocyte-macrophage colony stimulating factor; GM-CSF) within 14 days prior to or 14 days after CRS-207 infusion
- Prophylactic vaccines (e.g. pneumococcal vaccine, influenza vaccine) within 14 days prior to or after CRS-207 infusion

The following therapies should not be administered during the study unless medically necessary; approval must be obtained from the Medical Monitor for a subject to continue dosing if therapy is given concurrently with study participation:

- General anesthesia or deep sedation
- Aspirin >325 mg/day
- Acetaminophen > 4 g/day
- Systemic antibiotics

There are no prohibited therapies during the Follow-up Period.

If subjects receive immunosuppressive medications on or after study, prophylactic antibiotics to prevent CRS-207 infection are strongly recommended for the duration of the treatment with the immunosuppressant (recommended oral 80 mg trimethoprim / 400 mg sulfamethoxazole once daily or 160 mg trimethoprim / 800 mg sulfamethoxazole (DS) three days a week).

7.3.9 Treatment Compliance

Study treatments will be administered by IV infusion by a qualified health care professional at an approved study site. The date, time, and volume of each dose of study drug administered to each subject must be recorded in the dispensing log for the study and the eCRF.

Antibiotics will be provided to subjects following the last dose of CRS-207 as indicated in Table 2-1 or Table 2-2. Site personnel will contact the subject to confirm compliance with antibiotic treatment; subjects will be required to record self-administration of antibiotics in a diary.

7.4 Study Assessments and Procedures

Screening assessments will be conducted to confirm eligibility and to obtain baseline measurements; screening must be completed within 28 days prior to first dose of study drug. An enrollment form will confirm subject eligibility after completion of all screening procedures. Subjects must initiate dosing of study drugs within 2 weeks of completed enrollment.

The Treatment Period consists of multiple clinic visits during the initial four dosing cycles followed by treatment continuation, and an EOT visit.

The Follow-up Period begins when subject has discontinued/completed treatment and completed the EOT visit. The subject will be contacted every 3 months during the Follow-up Period to obtain information on any subsequent cancer-related treatments and/or survival.

All study visits (and visit windows), assessments, and procedures will be performed as indicated in the Schedule of Events (Table 2-1 or Table 2-2). Further details of study procedures and assessments can be found in the Study Reference Manual.

7.4.1 General Assessments

7.4.1.1 Informed Consent

Before screening assessments are conducted, an individual must be given a complete explanation of the purpose and requirements of the study; an informed consent form (ICF) approved by the Institutional Review Board (IRB)/Ethics Committees (EC) and an authorization for use and disclosure of protected health information must be signed before any study-specific procedure is performed. However, assessments done as part of standard of care prior to informed consent may be used if they are within the required Screening Period. An original signed consent form will be retained in the subject's source documentation at the site; a copy will be provided to the subject.

7.4.1.2 Eligibility

Potential subjects will be evaluated for entry into the study according to the stated inclusion and exclusion criteria (Section 7.2). Individuals deemed ineligible for study enrollment do not need to complete all screening procedures. The reason for ineligible status will be documented. Tests with results that fail eligibility requirements may be repeated once during the Screening Period if the Investigator believes the results to be in error. Additionally, a subject who fails screening may repeat the screening process 1 time if the Investigator believes there has been a change in eligibility status (e.g. after recovery from an infection).

For subjects who meet all inclusion/exclusion criteria, an enrollment form will be completed and sent to Sponsor or designee for review and approval. All screening assessments must be completed within a 3-week period; treatment must be initiated within 2 weeks of approved enrollment.

7.4.1.3 Demographics, Medical History, and Height

Demographic data and a complete medical history will be collected at screening by the Investigator or qualified designee. Demographic information (as allowed by local regulations) will include date of birth, age, gender, ethnicity, and race. Medical history should include all active conditions and any condition considered to be clinically significant by the Investigator. Medical and surgical history, and concurrent illnesses will be coded using the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) v.4.03. Details regarding the disease for which the subject has enrolled in this study (e.g. date of diagnosis, primary tumor histology, prior surgery(ies), radiation therapy, and stage of cancer) will be recorded.

Height (without shoes) will be obtained at screening with a stadiometer. Body mass index will be derived using height and weight.

7.4.1.4 Archived Tumor Tissue and Tumor Biopsies

Archived tumor tissue (paraffin embedded block or unstained charged slides) will be collected (if available) and may be used for analysis to confirm predominantly epithelial histology. Archived

samples should be submitted with a pathology report; personal identifying information must be redacted.

An image assisted core needle biopsy using standard techniques will be obtained from the primary tumor site(s) and/or accessible metastatic lesions 1) at screening (baseline) and 2) a paired biopsy during treatment (Cycle 2 Day 15 post CRS-207 and pembrolizumab administration). An additional biopsy may be requested at the time of disease progression (EOT visit). The Cycle 2 Day 15 biopsy should not be collected until at least 7 days have passed since CRS-207 administration, but no later than Day 15 of cycle to allow sufficient recovery time prior to next CRS-207 administration. The tissue sample should have proper size to enable IHC analysis of PD-L1. Fine needle aspirations will not be acceptable. If a subject's tumor is thought to be unsafe for biopsy by the Investigator, the site must discuss with the Medical Monitor prior to enrollment in study. If additional biopsies or relevant samples (e.g. pleural fluid) are collected for routine care during course of study, a sample should be retained if possible for Sponsor research evaluation. Detailed instructions for tissue collection, processing and shipment are provided in the Laboratory Manual.

Paired tumor biopsies and archival tissue will be analyzed for PD-L1 expression as well as other immune checkpoint molecules and infiltration of immune cells (e.g. T cell, myeloid and DC subpopulations) by IHC and gene expression profiling. PD-L1 expression may predict response to anti-PD-1 (Topalian, 2012; Brahmer, 2010). PD-L1 is also upregulated in response to IFN-γ released by infiltrating T cells and could potentially be a predictor of response to any active immunotherapy. Characterization of immune checkpoint expression as well as immune infiltrates may be predictive of response to therapy and may also give insight into next generation combinatorial approaches.

7.4.2 Efficacy Measures

Efficacy will be evaluated by changes in tumor burden, pulmonary function, and survival. The assessments that will be performed throughout the study to derive primary, secondary, and exploratory efficacy variables are described below and will be conducted according to the Schedule of Events in Table 2-1 or Table 2-2. Efficacy endpoints and associated analyses are described in Section 7.5.5.

7.4.2.1 Tumor Imaging and Response Assessments

CT scans of the thorax and abdomen will be performed at screening (pre-treatment baseline assessment) and up to 7 days prior to dosing every other cycle starting at Cycle 3 and throughout the Treatment Period. If CT scan is contraindicated (e.g. allergy to contrast dye), a MRI should be performed. Subjects with previously treated brain metastases must have a brain CT scan done within 14 days prior to first dose of study drug to confirm negative for new brain metastases. Radiographic tumor evaluation should include CT of all affected sites.

For each scan, tumor measurements should be obtained using modified RECIST for MPM and assessment of response will be determined by the local Investigator. The method of assessment and technique should be consistent throughout the study to enable characterization of each identified and reported lesion.

If radiographic disease progression is observed, another scan should be done at least four weeks later to confirm disease progression prior to treatment discontinuation. If a subject discontinues treatment without progressive disease (PD), Evaluation Visits with CT scan/tumor assessments should be completed every 6 weeks until documented disease progression.

Additional supportive analyses may be performed separately by an independent reviewer using objective disease responses definitions based on RECIST v1.1 and/or immune related response criteria (irRC). Sites must submit a copy of each scan on CD or other image media to the Sponsor; all protected health information (e.g. name, medical record number, etc.) must be redacted. Additional instructions for submission of scans are located in the Study Reference Manual.

7.4.2.2 Pulmonary Function Testing

Spirometry will be administered in accordance with American Thoracic Society and European Respiratory Society taskforce guidelines (Miller, Crapo, , 2005; Miller, Hankinson, , 2005) to assess pulmonary function. Spirometry will be performed with equipment at the study site; spirometry guidelines are provided in the Study Reference Manual. FVC is the pulmonary function variable. The percent predicted values will be calculated using published normative data (Hankinson, 1999) using height obtained at screening.

7.4.2.3 Survival Follow-Up

Following the Treatment Period, subjects will be contacted at 3 months intervals to assess survival and subsequent cancer-related therapies. Follow-up will continue until death of the subject, loss to follow-up, or close of study by the Sponsor. For subjects who withdraw from the study prior to completion of the Follow-up Period, reasonable efforts will be made to collect survival outcome. Sites will attempt to obtain vital status data from public records or other external sources where possible if a subject withdraws consent from study (i.e. refuse follow-up for vital status) or is documented as lost to follow up. All deaths must be reported on the eCRF.

The Sponsor may request survival status be assessed at additional time points during the course of the study. These additional contacts may be requested for safety review, interim analysis, and/or final analysis. All subjects who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

7.4.3 Safety Assessments

Safety assessments will be performed to characterize the safety of CRS-207 and pembrolizumab use in MPM. Safety will be assessed by collection of data on AEs, clinical laboratory

assessments, ECOG performance status, vital signs, weight, physical examination, electrocardiogram (ECG) parameters, and concomitant medications. Clinically significant changes from pre-treatment values in safety assessments should be reported as AEs. Safety assessments described below will be conducted according to the Schedule of Events (Table 2-1 or Table 2-2).

7.4.3.1 Eastern Cooperative Oncology Group Scale of Performance Status

The ECOG Scale of Performance Status is recognized as a standard tool to measure disease impact on daily living activities (Oken, 1982). The ECOG scale will be used by site personnel to determine eligibility and characterize a subject's level of functioning (self-care, daily activity, and basic physical ability) as indicated throughout the Treatment Period.

7.4.3.2 Vital Signs and Pulse Oximetry

Vital signs, including blood pressure, pulse rate, respiratory rate, and temperature and pulse oximetry will be performed at each indicated study visit. Vital signs will be obtained prior to, and immediately following each pembrolizumab infusion. Vital signs will be obtained prior to, every 30 minutes during the CRS-207 infusion and every hour during post-infusion follow-up. Subjects will be observed for at least 4 hours after the first CRS-207 infusion and the first cycle with same day dosing and at least 2 hours for each subsequent infusion. Pulse oximetry may be performed as clinically indicated.

Any clinically significant abnormal findings in vital signs or pulse oximetry should be recorded as an AE.

7.4.3.3 Physical Examination and Weight

Comprehensive Physical Examination

Complete physical examinations will be conducted at screening and EOT. Comprehensive physical examinations must be performed by a medically qualified individual such as a licensed Physician, Physician's Assistant, or an advanced Registered Nurse Practitioner, as local law permits. The comprehensive physical examination will include the following organ or body system assessments: skin; head, eyes, ears, nose, and throat; thyroid; lungs; cardiovascular system; abdomen (liver and spleen); extremities; lymph nodes; and a brief neurological examination. Before the first dose of study drug, clinically significant abnormal findings should be recorded as medical history. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

Symptom-directed Physical Examination

Symptom-directed physical examinations will be conducted at all other indicated visits (up to 3 days prior to dosing). The Investigator or medically qualified designee will perform a symptom-directed evaluation as clinically indicated. The targeted physical examination will include

assessment(s) of the body systems or organs, as indicated by subject symptoms, AEs, or other findings. New clinically significant abnormal findings should be recorded as AEs.

Weight will be obtained at each indicated visit, and prior to receiving any study drug. Any clinically significant abnormal findings in weight should be recorded as an AE

7.4.3.4 Adverse Events

AEs will be recorded from the time of first study drug administration until 28 days following the last dose of study drug or initiation of subsequent cancer-related therapy, whichever occurs first. If the EOT visit occurs less than 28 days from the last dose of study drug, the subject will be contacted 28 days (- 3 days) after the date of last study drug administration to complete the AE reporting period. A clinic visit or follow-up contact for AEs will also be conducted 1 day after each CRS-207 infusion (and one day after pembrolizumab infusions during cycles where CRS-207 is not administered). Contact must be documented in the study records.

All AEs and abnormal clinical laboratory assessments will be assessed for severity using the NCI-CTCAE v. 4.03. The determination, evaluation, reporting, and follow-up of AEs will be performed as outlined in Section 8.

7.4.3.5 Concomitant Medications

Medications used within 28 days prior to first dose of study medication will be recorded. A clinic visit or follow-up contact for concomitant medications will also be conducted 1 day after each CRS-207 infusion (and one day after pembrolizumab infusions during cycles where CRS-207 is not administered). All concomitant medication administered from Cycle 1 until the EOT visit will be recorded in the eCRF (including pre-medications and all over the counter medications). The generic name, dosage, duration, and reason for the concomitant medication should be included. Changes in the use of concomitant medications will be captured at each study visit.

7.4.3.6 Electrocardiogram

At indicated visits routine 12-lead ECGs will be performed. ECGs should be performed after the subject has rested for ≥5 minutes. For consecutive-day dosing, ECGs will be performed prior to each dose of study medication, immediately after the infusion, and at 1-hour post infusion. For visits where pembrolizumab and CRS-207 are administered on the same day, routine 12-lead ECGs will be performed prior to pembrolizumab infusion, immediately after pembrolizumab infusion, immediately after CRS-207 infusion, and at 1-hour post CRS-207 infusion. If abnormal at 1-hour post-infusion, repeat until baseline achieved. Additional ECGs may be performed if clinically indicated.

ECG parameters include heart rate, PR interval, QT interval, QRS duration, QTcF (Fridericia's correction), and QTcB (Bazett's correction). The ECG will be interpreted by the Investigator as

normal, not clinically significant abnormal, and clinically significant abnormal results. Clinically significant abnormal findings should be recorded as an AE.

7.4.3.7 Clinical Laboratory Evaluation for Safety

Routine hematology, serum chemistry, and urinalysis will be performed as a safety measure and to confirm dosing eligibility throughout the study (Section 7.4.4.2). The clinical significance of laboratory parameter findings will be determined by the Investigator throughout the study. The Medical Monitor may, depending on study criteria, be consulted before enrollment about a potential subject with abnormal laboratory values that are not considered clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. All abnormal laboratory values considered clinically significant by the Investigator must be recorded in the AE page of the eCRF. Any abnormal test that is determined to be an error does not require reporting as an AE.

7.4.4 Laboratory Assessments

A panel of laboratory assessments on blood and urine samples will be used to characterize the study population, and assess efficacy and safety throughout the Treatment Period. Assessments will be conducted per the appropriate Schedule of Events (Table 2-1 or Table 2-2).

7.4.4.1 Screening/Baseline-specific Laboratory Assessments

Blood samples will be obtained at screening to confirm eligibility and characterize immune status and prognostic tumor biomarkers for each subject and the study population. These initial laboratory assessments may be conducted at the institution's local laboratory and include:

- Virology screen for HIV antibody, hepatitis B surface antigen, and hepatitis C antibody
    - Hepatitis C viral load (if indicated)

7.4.4.2 Safety Laboratory Assessments

Routine hematology, serum chemistry, thyroid function tests, coagulation panels, and urinalysis will be conducted as a measure of safety and dosing eligibility per protocol requirements (Section 7.2.3). All clinical laboratory evaluations will be performed by the institution's local laboratory. Testing may be completed up to 3 days prior to each study drug administration. Fasting is not required. Additional tests may be performed if clinically indicated.

The following parameters will be evaluated at Screening and throughout the Treatment Period as indicated:

- Hematology: complete blood count (WBC, red blood cells, hematocrit, and hemoglobin) with differential including ANC, ALC and platelet count
- Serum chemistry: sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen, creatinine, lactate dehydrogenase, ALT, AST, alkaline phosphatase, bilirubin

(total, direct, indirect), total protein, albumin, calcium, magnesium, uric acid, and phosphate
- Coagulation panel: PT, INR, aPTT, D-dimers, fibrinogen
- Thyroid panel: triiodothyronine (T3) or free triiodothyronine (FT3), free thyroxine (FT4), and thyroid stimulating hormone (TSH)
- Urinalysis: bilirubin, blood, glucose, ketones, leukocytes, nitrite, pH, protein, and specific gravity (includes microscopy at Screening and EOT)

Pregnancy Testing and Contraception

The effects of CRS-207 and pembrolizumab on a fetus *in utero* or on the composition of sperm are unknown. Therefore WOCBP and fertile males must consent to use highly effective contraception [per (CTFG, 2014)] throughout the Treatment Period (or for 120 days after their final dose of study drug). Contraception must include at least one barrier method to minimize risk of fluid transmission.

A WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. For study eligibility, WOCBP must have negative pregnancy tests at screening and within 24 hours of first study drug administration. A serum pregnancy test (HCG) is required at screening; at all other indicated visits, only a urine pregnancy test is required. If a urine pregnancy test is positive, the results should be confirmed with a serum pregnancy test. Pregnancy of a subject or partner must be reported and followed (Section 8.4).

7.4.4.3 Blood for CRS-207 Surveillance

Blood samples will be collected from subject's peripheral vein and from the central line port, if applicable, at the EOT visit (prior to initiation of antibiotics) and at all visits indicated after EOT to monitor for presence of CRS-207. Subjects with samples positive for the presence of CRS-207 will be re-tested until negative results are confirmed.

7.4.4.4 Biomarker and Research Laboratory Assessments

Research assessments will be conducted on blood samples and tumor tissues and may help to characterize and monitor baseline and post-treatment immune responses mediated by CRS-207 and pembrolizumab. Samples required for laboratory evaluations will be collected and processed by sites as outlined in the Laboratory Manual. All analyses will be conducted by the Sponsor or the Sponsor's designee.

Exploratory assessments may include:

- Total CD4 and CD8 counts (will be done at Central Laboratory)

- Human leukocyte antigen (HLA) typing (type A and B of MHC Class I antigens; low resolution)
- Characterization of treatment induced immune responses including T cell responses to *Lm* and mesothelin,
- Immune cellular phenotyping and functional analyses of peripheral blood mononuclear cells (PBMCs) and tumor infiltrating lymphocytes
- Tumor biomarkers or prognostic factors (e.g. PD-1, mesothelin, plasma osteopontin, etc.)
- Circulating cytokines, chemokines, miRNA and other proteins.
- Gene expression profiling of PBMCs
- T cell receptor (TCR) profiling of PBMCs and tumors

Specific testing may include analysis for changes in protein analytes such as cytokines, antibodies, relevant tumor markers and markers of immune function by enzyme-linked immunosorbent assay (ELISA), or other relevant methods including peptide or protein arrays. In addition, assays of immune cell phenotyping and functions or responses may be conducted using whole blood samples and PBMCs. To explore whether a diverse T cell repertoire is predictive of response to therapy, sequencing of TCR genes may be performed on DNA isolated from peripheral blood and tumor to quantitate the composition of the T cell repertoire prior to and during therapy. Genetic markers associated with response or resistance may also be measured using peripheral blood DNA; peripheral blood DNA may also be used as a germline control to compare with tumor cell DNA. RNA isolated from peripheral blood for gene expression analysis may be used to characterize subjects who respond or are resistant to treatment. Additional assessments and methodologies may be used at the Sponsor's discretion.

7.4.5 Subset Studies

7.4.5.1 CRS-207 Shedding and Clearance Subset

A subset of 10 subjects from select sites in the US will undergo assessment of CRS-207 shedding and clearance as indicated in Table 2-1 or Table 2-2. Urine, rectal swab, and throat swab samples will be obtained pre-CRS-207, 4 hours (± 30 minutes) after the end of CRS-207 infusion, and 18-24 hours, and 7 days post-CRS-207 infusion. Clearance of CRS-207 in blood will be assessed pre-dose, and 18-24 hours, and 7 days post-CRS-207 infusion. Subjects with samples positive for the presence of CRS-207 will be re-tested until negative results are confirmed.

7.4.6 Appropriateness of Measures

Tumor imaging is the gold standard for assessing monitoring disease progression and tumor response in patients with cancer. The primary efficacy variable, ORR, is an accepted surrogate of efficacy appropriate for use in single-arm studies with smaller sample sizes. Tumor response will be evaluated using modified RECIST. Modified RECIST criteria for MPM was adapted to the growth pattern of MPM and has been shown to correlate with survival and lung function and is

used to measure outcomes (Byrne and Nowak, 2004). Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions, therefore radiologic disease progression should be confirmed by another scan at least 4 weeks after the initial scan and prior to discontinuing study drug.

Additional secondary efficacy variables will also be derived from tumor imaging and response assessments. Pulmonary function is compromised in patients with MPM; spirometry is routinely used to assess pulmonary function variables in this patient population. OS is the universally accepted direct measure of benefit and is an objective measure, although may be limited by difficulties with patient follow-up in smaller studies and confounded by non-cancer deaths in long-term studies.

The safety parameters to be evaluated in this study include standard assessments such as recording of medical history, AEs and SAEs, physical examination, vital signs, ECGs, serum chemistry and hematology, urinalysis, concomitant medications, and other routine clinical and laboratory procedures.

7.5 Statistical Analysis

The completeness of the data affects the integrity and accuracy of the final study analysis. Therefore, efforts will be made to ensure complete, accurate and timely data collection, and to avoid missing data. The procedures for handling missing, unused, or spurious data, along with the detailed method for analysis of each variable, transformations, and exploratory analyses will be presented in the Statistical Analysis Plan (SAP); the information below is intended as a guide to planned analyses.

7.5.1 Sample Size Determination

The sample size is based on an A'Hern single-stage phase 2 design (A'Hern, 2001). A sample size of 35 evaluable subjects are required to decide whether the proportion responding is less than or equal to 0.21 or greater than or equal to 0.40. If the number of responses is 12 or more, the hypothesis that P <= 0.21 is rejected with a target error rate of 0.05 (alpha). If the number of responses is 11 or less, the hypothesis that P >= 0.40 is rejected with a target error rate of 0.20 (power = 0.80).

The estimate of ORR from historical controls is based on a review of published literature, where Investigator-assessed response rates from 24% (Alley, 2015) to 28% (Quispel-Janssen, 2016) were reported.

7.5.2 General Considerations

All statements of statistical significance will be based on an overall two-tailed test at the 0.05 level of significance unless otherwise stated. Descriptive and inferential statistical methods will be used to summarize data. The term "descriptive statistics" refers to the number of subjects (n), mean, median, standard deviation, minimum, and maximum for continuous variables, and refers to the number and/or percentage of subjects (or events) for categorical variables. Summaries of time to event data from Kaplan Meier estimates will include the number of events, number of censored subjects, median and 95% confidence intervals.

All statistical analyses will be performed using SAS. The effects of noncompliance, dropouts, and covariates will be assessed to determine the impact on the general applicability of results from this study.

7.5.3 Subject Information

Subject disposition summaries will include the number of enrolled subjects, the number of subjects receiving study drug, the number of subjects completing the study, the number of subjects withdrawing prematurely, and the reasons for discontinuation.

Demographics and baseline disease characteristics will be summarized using descriptive statistics.

7.5.4 Analysis Sets

Evaluable Analysis Set (EAS) is defined as all subjects who received at least 1 dose of study treatment and were either assessed for response or were discontinued due to toxicity or clinical progression (or death due to clinical progression). The EAS will be used for analyses of the primary and secondary efficacy endpoints utilizing clinical response.

Full Analysis Set (FAS) is defined as all subjects who received at least 1 dose of study treatment. The FAS will be used for other analyses of efficacy (including pulmonary function and OS).

Safety Set includes all subjects who received any study treatment. All analyses of safety data will be conducted using the safety set.

Additional analysis sets (e.g. per protocol set) may be defined in the SAP.

7.5.5 Efficacy Analyses

All primary and secondary efficacy variables derived from tumor imaging and response assessments will be determined by the local Investigator using modified RECIST guidelines for MPM. Additional supportive analyses may be performed separately by an independent reviewer using objective disease responses definitions based on RECIST v1.1 and/or irRC.

7.5.5.1 Primary Efficacy Variable and Analysis

For the primary efficacy analysis, ORR is defined as the proportion of subjects with PR or CR according to modified RECIST for MPM. Subjects who discontinue due to toxicity or clinical progression prior to post-baseline tumor assessments will be considered as non-responders. Subjects who discontinue for other reasons prior to post-baseline tumor assessments will be replaced and not included in the primary efficacy analysis.

7.5.5.2 Secondary Efficacy Variables and Analyses

Secondary efficacy variables will be calculated for all subjects who receive at least one dose of study drug and are evaluable for response.

Secondary efficacy variables in the study include:

Disease control rate (DCR) defined as the percentage of subjects with CR, PR, or SD. Subjects who discontinue prior to post-baseline tumor assessments will be considered as non-responders.

Progression-free survival (PFS) is defined as the time from first dose of study drug until first documentation of disease progression or death due to any cause.

Subjects who do not experience disease progression and are alive on or before the data cut-off date will be censored at the time of last tumor assessment or data cut-off date, whichever is earlier. Subjects who do not experience disease progression and start new systemic anti-cancer therapy will be censored at the time the new systemic anti-cancer therapy was begun or the data cut-off date, whichever is earlier. Subjects with no assessments of disease progression will be censored at the time of receipt of first study drug. Subjects who are lost to follow-up for assessment of disease progression will be censored at their last tumor assessment or data cut-off date, whichever is earlier.

Pulmonary function improvement is defined as an increase in FVC from baseline of either ≥400 mL or ≥ 20%, assessed using spirometry.

The analysis of pulmonary function response will be based on the percent of subjects with documented improvement in pulmonary function variables. Assessments obtained after a switch to another anti-cancer therapy will be excluded from the analysis. Subjects who discontinue prior to post-baseline assessments will be considered non-responders.

Overall Survival (OS) defined as the time from first dose of study drug until date of death due to any cause. Subjects without documentation of death at the time of analysis will be censored as of the date the subject was last known to be alive, or the data cut-off date, whichever is earlier.

OS will be summarized using Kaplan-Meier estimates.

7.5.5.3 Other Efficacy Variables and Analysis

Additional efficacy analyses will be evaluated based on the following additional variables:

- Best Overall Response (BOR) defined as the subject's best objective disease response across all evaluable on-treatment assessments from all courses until another anti-cancer therapy has been introduced.
- Objective tumor response over time, and duration of response (DOR) defined as the time from first PR or CR until PD or death. DOR is defined as the time from the first tumor assessment that supports the subject's objective disease response to the time of disease progression or death due to any cause.
- Change from baseline in pulmonary function tests (FVC)

Exploratory analyses of the data will be conducted as deemed appropriate. Details of additional analysis of other variables are provided in the SAP.

7.5.6 Safety Analyses

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1 or higher and assessed for severity using the NCI-CTCAE v. 4.03. AEs will be summarized by system organ class and preferred term and presented in decreasing order of frequency.

Changes in clinical laboratory assessments, ECOG performance status, vital signs, weight, physical examination, ECG, and concomitant medications parameters from baseline to the EOT will be examined. Treatment-emergent changes from normal to abnormal values in key laboratory parameters will be identified. Laboratory data will be summarized for each time-point that specimens are collected. Changes in NCI toxicity grading will be presented using shift tables and listings of clinically significant values.

7.5.7 Research Laboratory Analyses

Analyses of research laboratory samples, tumor biopsies, and immune response data will be described separately outside the context of the SAP.

7.5.8 Timing of Analysis

The primary analysis will be performed following completion of enrollment and response assessments in the first 35 evaluable subjects. Information on survival will continue to be gathered and may be used for supplementary analyses after the completion of the final study report.

7.5.9 Data Monitoring Committee

There will be no formal Data Monitoring Committee for this study. Safety data including all unacceptable toxicities will be reviewed by a Safety Review Team comprised of participating investigators in the study, the Medical Monitor, and representatives of the Sponsor.

8 ADVERSE EVENT REPORTING

8.1 Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, occurring from the time of first study drug administration and up to 28 days after the last dose of study drug, whether observed by the Investigator or reported by the subject will be monitored and documented on the AE eCRF. Subjects should be instructed to report any AE that they experience to the Investigator. At each indicated visit, Investigators should make an assessment for AEs and record the event on the appropriate AE eCRF.

Wherever possible, a specific disease or syndrome rather than individual associated signs and symptoms should be identified by the Investigator and recorded on the eCRF. However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (e.g. surgery, endoscopy, tooth extraction, or transfusion) should be recorded as an AE, not the procedure.

Progression of the cancer under study is not considered an AE in this study. The term "disease progression" should be recorded as an AE/SAE only if there are no other identifiable AEs/SAEs associated with the disease progression at the time of reporting. For events associated with disease progression, the relevant signs and symptoms should be reported using a diagnosis whenever possible rather than individual underlying signs and symptoms. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE. If the events resulting from disease progression meet the criteria for an SAE (e.g. resulted in hospitalization, a life-threatening event, or death), the specific event(s) should be reported as an SAE(s). In both cases (i.e. AEs or SAEs related to disease progression), it should be indicated that each event (reported as a diagnosis or as signs and symptoms) is related to disease progression on the AE CRF.

Any medical condition already present prior to the first dose of study drug should be reported in medical history unless the medical condition or signs or symptoms present at baseline change in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (e.g. ECG) findings that are detected during the study or are present at screening and significantly worsen during the study should be reported as AEs. The Investigator will exercise his or her medical and scientific

judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Examples of AEs include the following:

- Significant or unexpected worsening or exacerbation of the indication under study
- Exacerbation of a chronic or intermittent preexisting condition, including an increase in frequency or intensity of the condition
- New conditions detected or diagnosed after investigational agent administration even if they were present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction with another medical product
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational agent or a concurrent medication.
    - For CRS-207: an overdose should not be reported as an AE or SAE; instead, the symptoms resulting from the overdose should be reported as the AE or SAE.

Examples of AEs do not include the following:

- Medical or surgical procedures (e.g. endoscopy, appendectomy); instead, the medical condition that led to the procedure is an AE
- Situations that are unwanted but in which an untoward medical occurrence did not occur (e.g. social inconvenience after admission to a hospital)
- Anticipated day-to-day fluctuations of a pre-existing disease or condition (present or detected before enrollment) that does not worsen overall

A follow-up is required for all subjects with AEs until the event has been resolved or the condition has stabilized. In case of unresolved AEs, including significant abnormal laboratory values at the EOT visit assessment, these events will be followed up until resolution or until they become clinically not relevant.

8.1.1 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE and the potential relationship between the AE and the study medication.

Assessment of Severity:

The severity of all AEs should be graded according to the NCI-CTCAE v. 4.03 (http://ctep.cancer.gov/reporting/ctc.html). For AEs not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with subject's daily activities
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with subject's usual activities, but still acceptable
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the subject's daily activities, unacceptable
- Life-threatening (CTCAE Grade 4): Life-threatening or disabling AE
- Death (CTCAE Grade 5): Death-related AE

Attribution:

The Investigator is obligated to estimate the relationship between the investigational agents and the occurrence of each AE or SAE using best clinical judgment. Other causes, such as the underlying disease, concomitant therapy, other risk factors, and the temporal relationship of the event to one or both of the investigational agents should be considered and investigated. The Investigator should consult the IB or product labeling information for marketed products in the determination of the assessment. The Investigator should consider all possible etiologies for the AE and render a causality assessment based on the most likely contributing factor to the AE.

There may be situations when an SAE has occurred and the Investigator has minimal information to include in the initial report. However, the Investigator must assess causality for every event before the transmission of the SAE. The Investigator may change his or her opinion of the causality in light of follow-up information, amending the SAE report.

The assessment of the relationship between the AE and the study medication will be determined using one of the following attribution categories as outlined in the NCI Guidelines: Adverse Event Reporting Requirements (2013).

RELATIONSHIP	**ATTRIBUTION**	**DESCRIPTION**
Unrelated to investigational agent/intervention	Unrelated	The AE *is clearly NOT related* to the intervention
	Unlikely Related	The AE *is doubtfully related* to the intervention
Related to investigational agent/intervention	Possibly Related	The AE *may be related* to the intervention
	Probably Related	The AE *is likely related* to the intervention

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
	Definitely Related	The AE *is clearly related* to the intervention

AEs listed as possibly, probably, or definitely related are considered to have a suspected "reasonable causal relationship" to the investigational agent/intervention (ICH E2A). The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship

8.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
    - NOTE: An AE or adverse reaction is considered "life-threatening" if, in view of either the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations;
    - NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e. no place to stay, live too far away to come for hospital visits) or for observation post-study drug administration will not be considered a SAE.
- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect; or
- An important medical event
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

8.3 Serious Adverse Event Reporting − Procedures for Investigators

8.3.1 Initial Reports

SAEs will be collected from the time of first study drug administration through 90 days following cessation of treatment, or 28 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. SAEs and events of clinical interest must be reported to the Sponsor (or designee) within 24 hours of the knowledge of the occurrence. Outside of the 90-day period, only SAEs considered related to the administration of study drug must be reported to the Sponsor.

In the event an SAE is observed or reported, the SAE report will be completed as thoroughly as possible including all available details about the event and the signature of the Investigator. If the Investigator does not have all information about an SAE, the Investigator will not wait to receive additional information before notifying the Sponsor of the event and completing the form. The form will be updated when additional information is received.

The SAE form in the electronic data capture (EDC) system should be completed for each SAE. Upon completion, designated study personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the EDC system, an email, telephone, or facsimile communication within 24 hours of awareness is acceptable. When the EDC system becomes available, the SAE information must be entered within 24 hours.

8.3.2 Safety Reporting Contact Information

Safety contact information may be found in the Study Reference Manual.

8.3.3 Expedited Reporting Requirements

The Sponsor (or designee) will report all SAEs that are unexpected and considered related to the administration of the investigational agent to the appropriate health and regulatory authorities and Investigators in the form of an expedited safety report within 15 calendar days after receiving information on the SAE. The Investigators will notify their reviewing IRB/EC and other committee(s) as required by institutional policies.

The Sponsor will also report to the appropriate health and regulatory authorities by facsimile, e-mail, or phone within 7 days of receiving the information, any unexpected life-threatening or fatal SAEs that are considered related to the investigational agent.

8.3.4 Follow-Up Reports

The Investigator must continue to follow the subject until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the subject dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (e.g. subject discharge summary or autopsy reports) via fax or e-mail to the Sponsor or designee.

8.4 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported following SAE reporting procedures in Section 8.3. All ECIs must be reported for the duration of the study regardless of causality.

Events of clinical interest for this trial include:

- [redacted]
- An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.

8.5 Adverse Events of Special Interest

Suspected infection with CRS-207 and/or *Listeria* are considered adverse events of special interest (AESI) and should be reported following SAE reporting procedures in Section 8.3. All AESIs must be reported for the duration of the study regardless of causality.

In the event a subject has a positive Listeria test at any time during or after study participation (except within 7 days after a CRS-207 infusion), the event should be reported to the Sponsor within 24 hours of the event.

8.5.1 Confirmed Listeria Infection

In the event a subject has a positive Listeria culture at any time during or after study participation (except within 7 days after a CRS-207 infusion), Sponsor should be notified within 24 hours of the event.

If Listeria has been confirmed at the clinical site or an external laboratory, all efforts should be made to obtain and ship the bacterial isolate from the original positive culture to the Sponsor or designee for strain confirmation; records on all samples cultured during this period must be obtained and provided to the Sponsor. Refer to the Laboratory Manual for shipping instructions.

8.5.2 Suspected (Unconfirmed) Infection with CRS-207 or Listeria

In the case of a suspected persistent CRS-207 or Listeria infection that has not been confirmed by culture, collection of blood, urine and stool samples in duplicate is recommended. One set of samples should be cultured locally for Listeria per institutional guidelines. Culture of cerebrospinal fluid should be obtained for subjects with suspected central nervous system infection. In such instances, analysis of cerebrospinal fluid should also include cell count, protein, glucose, and Gram stain. If samples are positive for Listeria, the Sponsor must be notified immediately, and the duplicate samples and positive listeria isolate must be sent to Sponsor or designee for strain confirmation. Instructions on collection, storage and shipping of samples for CRS-207 testing are provided in the Laboratory Manual.

If infection with CRS-207 is confirmed or suspected, IV antibiotics (Section 7.3.6.1) should be initiated as soon as possible and follow-up samples obtained for testing periodically to confirm absence/clearance of any CRS-207 infection. The Medical Monitor should be consulted regarding continuation of study drug treatment and treatment of suspected or confirmed infection.

8.6 Pregnancy Reporting

If the subject or partner of a subject participating in the study becomes pregnant during the study or within 120 days of discontinuing study drug (or 30 days if the subject initiates new anticancer therapy, whichever is earlier) the Investigator should report the pregnancy within 24 hours of being notified. Designated safety personnel will then forward the Exposure In Utero form to the Investigator for completion.

A subject becoming pregnant while on study drug will immediately be withdrawn from the study and EOT study procedures will be performed.

The subject or partner should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify designated safety personnel. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. SAE reporting procedures should be followed if the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e. postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly).

9 DATA MANAGEMENT AND RECORD KEEPING

9.1 Data Handling

Data will be recorded at the site on eCRFs and reviewed by the clinical research associate (CRA) during monitoring visits. The CRA will verify data recorded in the EDC system with source documents. All corrections or changes made to any study data must be appropriately tracked in an audit trail in the EDC system. An eCRF will be considered complete when all missing, incorrect, and/or inconsistent data has been accounted for and electronically signed by the Investigator or assignee.

Data will be processed using a validated computer system conforming to regulatory requirements.

9.2 Data Entry

Data must be recorded using the EDC system as the study is in progress. All site personnel must log into the system using their secure user name and password in order to enter, review, or correct study data. These procedures must comply with Title 21 of the Code of Federal Regulations (21 CFR Part 11) and other appropriate international regulations. All passwords will be strictly confidential.

9.3 Medical Information Coding

For medical information, the following thesauri will be used:

- Latest version of MedDRA (version 18.1 or higher) for medical history and AEs, and
- World Health Organization Drug Dictionary Enhanced (Sept. 2015 or later) for prior and concomitant medications.

9.4 Data Validation

Validation checks programmed within the EDC system, as well as supplemental validation performed via review of the data, will be applied to the data in order to ensure accurate, consistent, and reliable data. Data identified as erroneous, or data that are missing, will be referred to the site for resolution through data queries.

The eCRFs must be reviewed and electronically signed by the Investigator in order to be considered complete.

9.5 Record Keeping

Records of subjects, source documents, monitoring visit logs, eCRFs, inventory of study drugs, regulatory documents, and other Sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data

are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

10 INVESTIGATOR REQUIREMENTS AND QUALITY CONTROL

10.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve human subjects. Compliance with this standard provides public assurance that the rights, safety, and well-being of study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical study data are credible.

10.2 Investigator Requirements

Each Investigator must provide the Sponsor and/or its designee a completed and signed Form FDA 1572 and a Financial Disclosure Form. All sub-Investigators must be listed on Form FDA 1572 and Financial Disclosure Forms must be completed for all sub-Investigators listed on Form FDA 1572.

A Coordinating Investigator will be identified for multicenter trials conducted in the EU and Australia. The Coordinating Investigator will be selected on the basis of active participation in the trial, thorough knowledge of the therapeutic area being studied, and the ability to interpret data.

10.2.1 Disposition and Accountability of Investigational Products

The Investigator is responsible for the control of investigational products under study. An investigational product dispensing log must be kept current and should contain the following information:

- The identification number for each subject who is administered the investigational product
- The date(s) and quantity of the investigational product administered to the subject
- Documentation of proper disposal of used investigational product vials or unused vials subjected to temperature excursion
- Documentation of proper disposal (or return, at Sponsor's request) of unused investigational product vials.

The Investigator is responsible for investigational product accountability during on-site monitoring visits. All records and used/unused supplies of the investigational product must be available for inspection at every monitoring visit.

The study sites, per institutional guidelines, will destroy used investigational product vials after formulation for administration. The formulation of investigational product for administration and the destruction of each used vial will be documented in the investigational product accountability log. Unused investigational product will be destroyed at the study site after final investigational product accountability and notification by Sponsor, unless otherwise directed by Sponsor.

10.3 Institutional Review Board/Ethics Committee

The IRB/EC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of subjects. The study will only be conducted at sites where IRB/EC approval has been obtained. The protocol, IB, ICF, advertisements (if applicable), written information given to the subjects, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/EC by the Investigator.

Federal regulations and International Council on Harmonisation (ICH) require that approval be obtained from an IRB/EC prior to participation of subjects in research studies. Prior to study onset, the protocol, any protocol amendments, ICFs, advertisements to be used for subject recruitment, and any other written information regarding this study to be provided to a subject or subject's legal guardian must be approved by the IRB/EC.

No study drug will be released to the site for dosing until written IRB/EC authorization has been received by the Sponsor.

10.4 Informed Consent

The ICF and any changes to the ICF made during the course of the study must be agreed to by the Sponsor or designee and the IRB/EC prior to its use and must be in compliance with all ICH GCP, local regulatory requirements, and legal requirements.

The Investigator must ensure each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation and must ensure the subject has been informed of his/her rights to privacy. The Investigator will obtain written informed consent from each subject before any study-specific activity is performed and will document consent was obtained prior to enrollment in the study in the source documentation. The original signed copy of the ICF must be maintained by the Investigator and is subject to inspection by a representative of the Sponsor, auditors, the IRB/EC, and/or regulatory agencies. A copy of the signed ICF will be given to the subject.

10.5 Study Monitoring Requirements

To ensure the study is conducted in accordance with the protocol and ICH GCP, the study monitor will aid the Investigator and, at the same time, the Sponsor in the maintenance of complete, legible, well organized and easily retrievable data. Before the enrollment of any subject in this study, the Sponsor or their designee will review with the Investigator and site personnel the following documents: protocol, IB, eCRFs and procedures for their completion, informed consent process, study drug management, and the procedure for reporting SAEs.

The Investigator will permit the Sponsor or their designee to monitor the study as frequently as deemed necessary to determine that data recording and protocol adherence are satisfactory. During monitoring visits, information recorded on the eCRFs will be verified against source documents and requests for clarification or correction may be made. After the eCRF data are entered by the site, the monitor will review the data for safety information, completeness,

accuracy, and logical consistency. Computer programs that identify data inconsistencies may be used to help monitor the clinical study. If necessary, requests for clarification or correction will be sent to Investigators. The Investigator and his/her staff will be expected to cooperate with the monitor and provide any missing information, whenever possible.

All monitoring activities will be reported and archived. In addition, monitoring visits will be documented at the site by signature and date on the study-specific monitoring log.

10.6 Disclosure of Data

Data generated by this study must be available for inspection by health and regulatory authorities (such as FDA, Health Canada, European Medicines Authority, and others), the Sponsor or designee, and the IRB/EC as appropriate. Subjects or their legal representatives may request their medical information be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the study is confidential and disclosure to third parties other than those noted above is prohibited.

10.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or the Sponsor, the Investigator will keep records, including the identity of all participating subjects (sufficient information to link records, e.g. eCRFs and hospital records), all original signed ICFs, copies of all eCRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the Investigator according to specifications in the ICH guidelines, local regulations, or as specified in the Clinical Study Agreement, whichever is longer. The Investigator must obtain written permission from the Sponsor before disposing of any records, even if retention requirements have been met.

If the Investigator relocates, retires, or for any reason withdraws from the study, the Sponsor should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to the Sponsor.

10.8 Publication Policy

Following completion of the study, the data may be considered for publication in a scientific journal or for reporting at a scientific meeting. Each Investigator is obligated to keep data pertaining to the study confidential. The Investigator must consult with the Sponsor before any study data are submitted for publication. The Sponsor reserves the right to deny publication rights until mutual agreement on the content, format, interpretation of data in the manuscript, and journal selected for publication are achieved.

10.9 Financial Disclosure

Investigators are required to provide financial disclosure information to the Sponsor to permit the Sponsor to fulfill its obligations under 21 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.

10.10 Insurance and Indemnity

In accordance with the relevant national regulations, the Sponsor has taken out subject liability insurance for all subjects who have given their consent to the clinical study. This cover is designed for the event that a fatality, physical injury, or damage to health occurs during the clinical study's execution.

10.11 Legal Aspects

The clinical study is submitted to the relevant national competent authorities in all participating countries to achieve a clinical trial authorization (CTA).

The study will commence (i.e. initiation of study centers) when the CTA and favorable ethics opinion have been received.

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SIGNATURE PAGE

STUDY TITLE: A Phase 2 Single-arm Study to Evaluate Safety and Efficacy of CRS-207 with Pembrolizumab in Adults Previously Treated for Malignant Pleural Mesothelioma

We, the undersigned, have read Protocol ADU-CL-13 and agree it contains all necessary information required to conduct the study.

Signature	Date
Natalie Sacks	5 July 17

Natalie Sacks, MD
Chief Medical Officer
Aduro Biotech, Inc.

INVESTIGATOR AGREEMENT

STUDY TITLE: A Phase 2 Single-arm Study to Evaluate Safety and Efficacy of CRS-207 with Pembrolizumab in Adults with Previously-Treated Malignant Pleural Mesothelioma

By signing below I agree that:

I have read the protocol and agree it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provisions of this protocol and will make a reasonable effort to complete the study within the time designated. I will provide copies of this protocol and access to all information furnished by Aduro Biotech to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures. I will let them know this information is confidential and proprietary to Aduro Biotech and may not be further disclosed to third parties. I understand that the study may be terminated or enrollment suspended at any time by Aduro Biotech, with or without cause. I have the right to suspend enrollment of subjects at my study site if necessary to protect the best interests of the study subjects.

I agree to conduct this study in full accordance with United States Food and Drug Administration Regulations, Institutional Review Board/Ethics Committee Regulations, and International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices.

_____ _____

Investigator's Signature Date

_____

Investigator's Printed Name