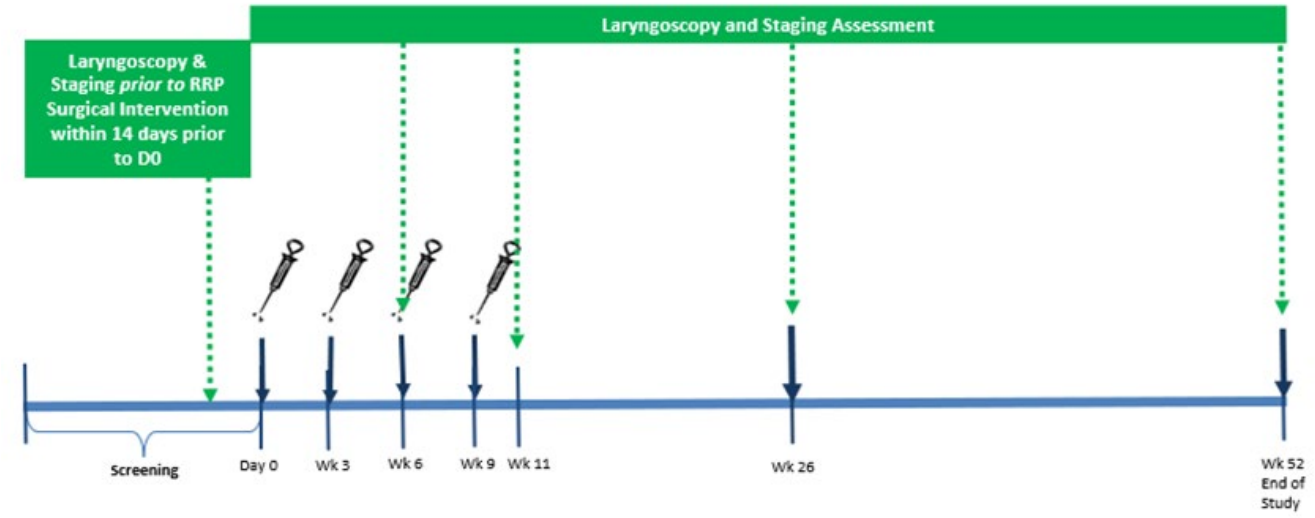
Supplementary Figure 1. RRP-001 Clinical Trial Study Design



Abbreviations: D0 = Day 0; RRP = recurrent respiratory papillomatosis; WK = week.

RRP-001 (ClinicalTrials.gov identifier: NCT04398433) was a Phase 1/2, single-arm, open-label study. The study was a single dose-level trial using a safety run-in, whereby up to 6 patients were to be enrolled, with a one-week waiting period between each patient. Each patient was assessed up to Week 6. Once the first 3 patients had completed Week 6 assessments, in the absence of dose-limiting toxicity (DLT), enrollment could begin in full. However, if a single patient had a DLT prior to the first 3 to 6 patients completing Week 6, enrollment was limited to 6 patients until all 6 had undergone Week 6 DLT assessment. If a second patient within the first 6 experienced a DLT within the first 6 weeks, enrollment would stop, and the Medical Monitor and Investigator(s) at the patients' site(s) would discuss the case and decide whether to cease further enrolment. DLTs were defined as Grade ≥3 hematologic or non-hematologic toxicities (graded per the National Cancer Institute's Common Terminology Criteria for Adverse Event [CTCAE] version 5.0) that did not respond to supportive therapy and lasted for longer than 48 hours.

Dose Limiting Toxicity (DLT) Definition

Tolerability was determined by the reported incidence of dose-limiting toxicity (DLT), which was defined as:

- Treatment-related NCI Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) Grade ≥3 non-hematological toxicity that does not respond to supportive therapy and lasts for longer than 48 hours, or;
- Treatment-related NCI CTCAE v5.0 Grade ≥3 hematological toxicity that does not respond to supportive therapy and lasts for longer than 48 hours.

RRP-001 Inclusion and Exclusion Criteria

Each subject was required to meet all the following criteria to be enrolled in the study:

- Provide written Institutional Review Board–approved informed consent in accordance with institutional guidelines.
- Be aged ≥18 years on the day of signing the informed consent and be able and willing to comply with all trial procedures.
- Have histologically documented human papillomavirus (HPV)-6 or HPV-11–positive respiratory papilloma or documentation of low-risk positive HPV using a Sponsor-approved HPV-6 or HPV-11 type-specific assay.
- Have a requirement for frequent recurrent respiratory papillomatosis (RRP) intervention in order to remove or resect respiratory papilloma, as defined as at least 2 RRP surgical (including laser) interventions in the year prior to and including day 0.
- Be an appropriate candidate for upcoming surgical intervention per investigator judgement and RRP Staging Assessment score.
- Have adequate bone marrow, hepatic, and renal function, as defined by: absolute neutrophil count) ≥1000 cells/mm^3, platelets ≥50,000/mm^3, and hemoglobin ≥9 g/dL; concentrations of total serum bilirubin within 1.5 × upper limit of normal (ULN), aspartate aminotransferase and alanine aminotransferase levels within 1.5 × ULN, and serum creatinine ≤1.5 × ULN.
- Agree that during the trial, male participants will not father a child, and female participants cannot be or become pregnant if they are of child-bearing potential.
- Subjects must meet one of the below requirements:
    - Be of nonchildbearing potential (≥12 months of nontherapy-induced amenorrhea, confirmed by follicle stimulating hormone, if not on hormone replacement).

- Be surgically sterile (vasectomy in males or absence of ovaries and/or uterus in females).
- Agree to use one highly effective or combined contraceptive methods that result in a failure rate of <1% per year during the treatment period and at least through week 12 after last dose. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Agree to abstinence from penile-vaginal intercourse when this is the subject's preferred and usual lifestyle.

Subjects meeting any of the following criteria will be excluded from the study:

- Receipt of therapy directed toward RRP disease (other than surgery or ablation), including but not limited to antivirals (including cidofovir), radiation, chemotherapy, anti-angiogenic therapy (including bevacizumab), prophylactic HPV vaccination (including Gardasil) as therapeutic intervention, or therapy with an experimental agent within 3 months prior to day 0.
- Have ongoing or recent (within 1 year) evidence of autoimmune disease that required treatment with systemic immunosuppressive treatments, with the exception of: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that requires only hormone replacement, or psoriasis that does not require systemic treatment.
- Have a diagnosis of immunodeficiency or treatment with systemic immunosuppressive therapy within 28 days prior to the first dose of trial treatment, including systemic corticosteroids.
- Have a high risk of bleeding or require the use of anti-coagulants for management of a known bleeding diathesis.

- Receive any live virus vaccine within 4 weeks prior to first dose of trial treatment or any nonlive vaccine within 2 weeks prior to the first dose of trial treatment.
- Have a history of clinically significant, medically unstable disease that, in the judgment of the Investigator, would jeopardize the safety of the subject, interfere with trial assessments or endpoint evaluation, or otherwise impact the validity of the trial results. This may include chronic renal failure; myocardial ischemia or infarction; New York Heart Association class III/IV cardiac disease; any cardiac preexcitation syndromes (such as Wolff-Parkinson-White, cardiomyopathy, or clinically significant arrhythmias); current malignancy with the exception of treated basal or squamous cell skin cancers, prostate cancer, or carcinoma of the cervix in situ; human immunodeficiency virus, which may impact the ability to mount an immune response to the study therapy; or drug or alcohol dependence.
- Have fewer than 2 acceptable sites available for intramuscular injection considering the deltoid and anterolateral quadriceps muscles. The following are unacceptable sites:
    - Tattoos, keloids, or hypertrophic scars located within 2 cm of intended treatment site
    - Cardioverter-defibrillator or pacemaker (to prevent a life-threatening arrhythmia) that is located ipsilateral to the deltoid injection site (unless deemed acceptable by a cardiologist)
    - Metal implants or implantable medical device within the intended treatment site.
- Be imprisoned or under compulsory detainment (involuntary incarceration) for treatment of either a psychiatric or physical (i.e., infectious disease) illness.
- Be pregnant or currently breastfeeding.

- As determined by the Investigator, have any medical or psychological or nonmedical condition that might interfere with the subject's ability to participate or affect the safety of the subject.