2.0 Synopsis

<table>
<tr><td>Name of Sponsor:
VACCIBODY A.S.
Oslo Research Park
Gaustadalléen 21, 0349 Oslo
Norway</td><td rowspan="3">Individual study table referring to part of the dossier

Volume:

Page:</td><td rowspan="3">(For national authority use only)</td></tr>
<tr><td>Name of finished product:
VB10.16</td></tr>
<tr><td>Name of active ingredient:
DNA plasmid pUMVC4a-VB10.16</td></tr>
<tr><td colspan="3">Title of the study:
VB C-01: An Exploratory Safety and Immunogenicity Study of Human Papillomavirus (HPV16^{+}) Immunotherapy VB10.16 in Women with High Grade Cervical Intraepithelial Neoplasia (HSIL; CIN 2/3)</td></tr>
<tr><td colspan="3">Investigators and study centers:
This was a multicenter study that involved 4 participating sites in Germany.

The investigators were:
Prof Peter Hillemanns (Principle Investigator)
Prof Karl Ulrich Petry
Prof Linn Wölber
Dr Gerd Böhmer</td></tr>
<tr><td colspan="3">Publication (reference): N/A</td></tr>
<tr><td colspan="2">Study period (years): 2015-2019
First patient on-study date: 08 September 2015
Study end date: 17 January 2019</td><td>Clinical phase: I</td></tr>
<tr><td colspan="3">Objectives:
<u>The primary objective was:</u>
• To assess the safety/tolerability of 3 mg VB10.16 immunotherapy in patients with HPV16^{+} Cervical Intraepithelial Neoplasia Grade 2/3 (CIN 2/3).

<u>The secondary objectives were:</u>
• To assess immunogenicity of 3 mg VB10.16 immunotherapy in patients with HPV16^{+} Cervical Intraepithelial Neoplasia Grade 2/3 (CIN 2/3).
• To make a preliminary assessment of efficacy of VB10.16 immunotherapy.</td></tr>
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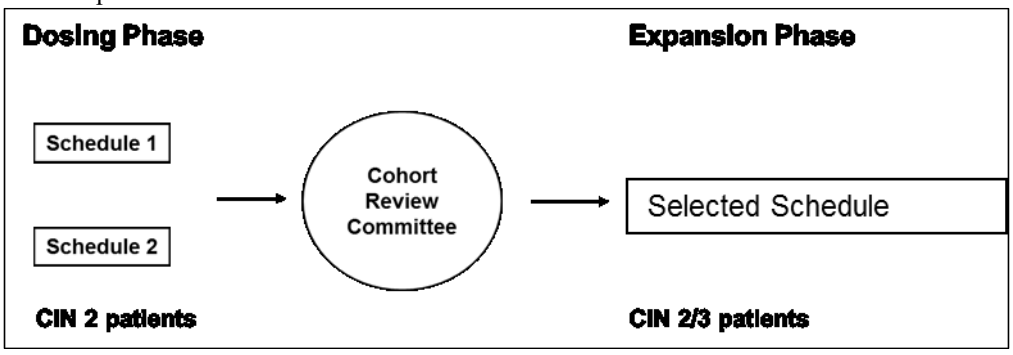
Methodology:

This was an exploratory, open label, multicenter study of VB10.16 immunotherapy in patients with high grade HPV16$^+$ Cervical Intraepithelial Neoplasia (CIN 2/3), also described as high grade cervical intraepithelial neoplasia (HSIL).

The study was divided into 2 phases:

- The Dosing Phase evaluated safety/tolerability and immunogenicity of different vaccination schedules of 3 mg VB10.16. Two different vaccination schedules were tested. Each Cohort consisted of 8 screened patients and overall this resulted in a total of 16 enrolled patients.
- The Expansion Phase evaluated safety/tolerability, immunogenicity and early signs of efficacy of VB10.16 with the selected vaccination schedule (Schedule 1). Eighteen patients were enrolled in this phase.



Synopsis figure: Two phase design of the exploratory study: Dosing Phase and Expansion Phase with selected schedule.

Number of patients:

This study recruited 38 female patients with HSIL at 4 sites in Germany. Sixteen patients were treated in the Dosing Phase of the study to assess 2 different vaccination schedules of VB10.16. Twenty-two additional patients were enrolled in the subsequent Expansion Phase and 18 patients were treated. One of these 18 patients stopped treatment after 2 vaccinations, due to retrospectively determined screen failure (not HPV16 positive).

Inclusion criteria:

To be eligible to participate in this study, patients must have met the following inclusion criteria:

1. Women greater or equal than 18 years who, after counselling by their clinicians consider the risk to future pregnancies from treating cervical abnormalities to outweigh the risk of developing cancer during observation of those abnormalities. In this context no specific upper age threshold was intended at the time of clinical trial entry.
2. Women with ectocervical HPV16$^+$ associated HSIL as verified by local pathology (biopsy) obtained within 4 Weeks prior to start of treatment.
   - Dosing Phase: Women with histologically confirmed HPV16$^+$ associated CIN 2 HSIL.
   - Expansion Phase: Women with histologically confirmed HPV16$^+$ associated CIN 2/3 HSIL.
3. Satisfactory colposcopic examination documented with colpo-photography (digital photography) defined as:
   - Visibility of entire transformation zone including the squamocolumnar junction.

- Visibility of the entire lesion margin.

4. ECOG performance status smaller or equal than 1.
5. Written informed consent.
6. Agreed to mandatory biological sampling schedule in the study.

Exclusion criteria:
To be eligible to participate in this study, patients must not have met the following exclusion criteria:

Concomitant conditions

1. More than 2 cervical quadrants of CIN 3 as visualized by colposcopy.
2. Atypical glandular cells (AGC) or adenocarcinoma in situ (AIS) on cytology, malignant cells on cytology or histology or other suspicion of either micro-invasive or invasive disease.
3. Current severe pelvic inflammatory disease, severe cervicitis, or other severe gynecological infection as per colposcopy and clinical examination.
4. Positive serological test for hepatitis C virus or hepatitis B virus surface antigen (HBsAg) or human immunodeficiency virus (HIV).
5. Administration of any blood product within 12 weeks of enrollment.
6. Concomitant or prior malignant disease, with exception of adequately treated basal cell carcinoma or other non-melanomatous skin cancer, low grade bladder cancer or other malignancies treated with curative intent 2 or more years pre-study entry and in remission at study entry.
7. Clinically significant autoimmune disease.
8. Known allergy to kanamycin or other aminoglycosides.
9. Known immunodeficiency and or immunosuppression.
10. History of toxic shock syndrome.
11. Evidence or history of clinically significant cardiac disease including congestive heart failure, unstable angina, acute myocardial infarction or cerebrovascular accident within the last 6 months, and symptomatic arrhythmia requiring therapy (with the exception of extra systoles or minor conduction abnormalities and controlled and well treated chronic atrial fibrillation).
12. Active infection requiring parenteral antibiotics.
13. Tattoos, scars, or active lesions/rashes within 2 cm of the site of vaccination or any implantable leads.

Current and prior treatment

14. Immunosuppression including the continued use of systemic or topical steroids at or near the administration site [deltoid, upper arm] (excluding inhaled and eye drop-containing corticosteroids) or the use of immunosuppressive agents for any concurrent condition. All other corticosteroids must be discontinued more than 4 weeks prior to first study vaccine administration.
15. Major surgery within 3 months of trial entry.
16. Current or recent (within 30 days of the first study treatment) participation in a clinical trial or treatment with another investigation medicinal product.

17. Previous vaccination (either therapeutic and/or prophylactic) against HPV.
18. Administration of any live vaccine within 90 days of trial entry.
19. Concomitant anticancer therapies.

Hematology, coagulation and biochemistry:

20. Inadequate bone marrow function:
    - Absolute Lymphocyte Count: less than 0.8 x 10^9/L.
    - Platelet count less than 100 x 10^9/L or hemoglobin less than 6 mmol/L (transfusion allowed up to 12 weeks prior to screening).
21. Inadequate liver function:
    - Serum total bilirubin greater than 1.5 x the Upper Limit of Normal (ULN) for the institution.
    - Aspartate Amino Transferase (AST) or Alanine Amino Transferase (ALT) greater than 3.0 x ULN.
    - Alkaline phosphatase levels greater than 5.0 x ULN.
22. Clinically significant uncorrected electrolyte abnormalities (Sodium, Potassium, Magnesium, and Phosphate) that were greater than common terminology criteria for adverse events (CTCAE) grade 3 for both low and high values.

Other

23. Female patients of childbearing potential not willing to use an effective form of contraception during treatment and for at least 6 months after the last dose of VB10.16.

    Effective forms of contraception included (if using hormonal contraception, this method must be supplemented with a barrier method, preferably male condom):
    - Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
      - oral
      - intravaginal
      - transdermal
    - Progestogen-only hormonal contraception associated with inhibition of ovulation:
      - oral
      - injectable
      - implantable
    - Intrauterine device (IUD)
    - Intrauterine hormone-releasing system (IUS)
    - Bilateral tubal occlusion
    - Vasectomized partner
    - True sexual abstinence defined as when this was in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal were not acceptable methods of contraception.

24. Pregnancy or intention to become pregnant during the study period. Urine or serum pregnancy test were to be performed during screening, prior to each vaccination, at Visit 6 (Week 24), Visit 7 (Month 9) and Visit 8 (Month 12) after the first vaccination.
25. Nursing women.
26. Evidence of any other medical conditions (such as psychiatric illness, infectious diseases, physical examination or laboratory findings) that may have interfered with the study participation, affect patient compliance or place the patient at high risk from treatment-related complications.

Test product, dose and mode of administration, batch number:

Investigational Medicinal Product (VB10.16)
VB10.16 is a naked DNA plasmid vaccine. The IMP was supplied as a sterile, ready to use solution at a concentration of 3 mg/mL in 1 mL glass vials. The vials had to be stored below -20 °C. A single batch of VB10.16, batch number COBb002, was used throughout.

Formulation
Three mg/mL in phosphate buffered saline pH 7.4.

Medical Device for Vaccination
The vaccination device for intramuscular administration was supplied by Vaccibody A.S. as PharmaJet® Stratis 0.5 mL Needle-free Injection System (510(k) Number: K111517; CE Number: 556625).

Route of Administration
The IMP was administered using the PharmaJet® Stratis 0.5 mL needle-free injection system to deliver the plasmid intramuscularly (IM) in the area over the lateral deltoid muscle. The delivery volume was 0.5 mL per injection. Two injections were administered at each vaccination time point. The 2 injections were given in different arms.

Duration of treatment:
Patients were screened during a maximum period of 6 weeks before study entry. Eligible patients received 3 vaccinations of VB10.16 in the Dosing Phase and 4 vaccinations in the Expansion Phase at pre-specified time points. One of the Expansion Phase patients stopped treatment after 2 vaccinations, due to retrospectively determined screen failure.

Patients were followed every 8 weeks for 24 weeks by colposcopic evaluation (digital photography) including cytology and $HPV16^+$ testing. Blood sampling was performed at pre-specified time points in all patients to monitor cellular immune response in the blood. The local tissue immune response was analyzed by comparing representative biopsies of cervical lesions obtained at screening, and during follow up. The clinical response was monitored by colposcopy, cytology, HPV status and histology.

After Visit 6 (Week 24), the disease status (Colposcopy: no CIN, CIN 1, 2 or 3; Treatment: therapeutic resection: yes or no, Histology: p16 immunohistochemistry (IHC)), ECOG, HPV status and any potential late-emerging safety events were documented in an extended follow up, up to Visit 8 (Month 12).

Criteria for evaluation
Safety assessments
Patients were assessed for safety at screening, as well as during treatment and follow up. AEs and Serious Adverse Events (SAEs) regardless of suspected relationship to study treatment were recorded from the time the patient

consented to the study until up to 30 days after the last vaccination with VB10.16. After this period only those AEs and SAEs that were considered related to the study treatment or events considered significant for any other reason were reported. Potential late-emerging adverse events (LEAEs) considered related to study treatment were recorded during the extended follow up period, up to Visit 8 (Month 12).

Safety was assessed by means of physical examination, vital signs, performance status, laboratory evaluations (hematology, biochemistry), recording of concurrent illness/therapy and AEs.

Definition of dose limiting toxicity

A Dose Limiting Toxicity (DLT) was defined as a clinically significant toxicity or abnormal value assessed as unrelated to the underlying disease, or concomitant medication and considered related to the study treatment. DLTs were assessed for all patients during the DLT observation period and graded according to the National Cancer Institute (NCI) CTCAE Version 4.0.

- All Grade 3 and 4 toxicities which were clinically unexpected and causally related to VB10.16 and occured within 30 days after the last vaccination.

Efficacy assessments

Immunogenicity:

- The characterization of the cellular immune response against the E6/E7 viral antigen.
  - Systemic T cell response measured by $HPV16^+$ E6/E7 IFN-γ enzyme-linked immunospot assay (ELISpot).
  - Flow cytometry analysis (FACS) of cellular surface markers and intracellular cytokine staining.
  - IHC to assess T cell infiltration in cervical tissue samples.
- Exploratory analysis of additional potential relevant markers such as PD-L1 status (programmed death ligand 1), FOXP3 (forkhead box P3), CCR5-Δ32 mutation (C-C chemokine receptor type 5), HLA typing (human leucocyte antigen).

HPV Regression:

- Analysis of $HPV16^+$ infection at screening and after Visit 4 (Week 8), Visit 5 (Week 16) and Visit 6 (Week 24).

CIN Regression:

- Colposcopy evaluation at screening after Visit 4 (Week 8), Visit 5 (Week 16) and Visit 6 (Week 24).
- Histological grading of CIN lesions based on the pathological assessment of representative biopsies at screening, after Visit 5 (Week 16) and Visit 6 (Week 24).

Statistical methods

Analysis populations

Safety Evaluable Population:

All patients who received any amount of VB10.16 are included in the safety evaluable population. This population was used to describe safety, drug administration data and demographics, baseline data.

Efficacy Evaluable Population:
All evaluable patients with at least one post-baseline colposcopic assessment and positive HPV16 COBAS test are included in the efficacy evaluable population. This population was used to summarize the efficacy-related endpoints.

Immunogenicity Evaluable Population:
All evaluable patients with an immunologic assessment performed during the study are included in the immunogenicity evaluable population. This population was used to summarize the immunogenicity-related endpoints.

Safety analysis
Safety analyses are based on the safety evaluable population. Descriptive statistics are used to summarize the safety parameters. The number of patients with VB10.16 administrated was summarized by Cohort and overall, using frequency counts, and the number and percentage of the vaccinations. Study vaccine injection site, date, time and total dose are listed by Cohort for applicable visits. Dose Limiting Toxicity (DLT) was defined as a clinically significant toxicity or abnormal value assessed as unrelated to the underlying disease, or concomitant medication and considered related to the study treatment. The DLT observation period was 30 days after the final vaccination. DLTs were assessed by dose Cohort for all patients during the DLT observation period and graded according to CTCAE Version 4.0.

Immunogenicity analysis
Immunogenicity analyses were performed on the immunogenicity evaluable population. T cell response and B-cell response are listed.

- The number (%) of patients with an E6/E7 specific cellular immune response in the blood.
- The number (%) of patients with cellular immune response in the target lesions.

The quantitative change from baseline at each scheduled timepoint was summarized by dose Cohort for each immunological parameter using descriptive statistics.

Efficacy analysis
Efficacy analyses were performed on the efficacy evaluable population for each available assessment. The number and percentage of patients with HPV16 clearance, along with their 95% confidence intervals, were calculated using the Clopper-Pearson method by dose Cohort. The number and percentage of cervical intraepithelial neoplasia (CIN) categorization, and response assessment by visit were summarized by dose Cohort. Change from baseline in percent of total area affected by visit was summarized by dose Cohort. Percent change from baseline in total area affected overtime (Spider plot) was provided for each Cohort. Responses assessment (CR, PR, SD, PD, NE, NA) were captured on a case report form (CRF) CIN regression assessment page. Overall response was counted once and summarized as the number (%) of patients in each response category. The overall response rate (ORR) was defined as the proportion of patients with a best overall response of CR or PR. Disease Control Response (DCR) was defined as the proportion of patients with a best overall response of CR or PR or SD. The two-sided 95% Clopper-Pearson confidence intervals were calculated for ORR and DCR using the following Statistical Analysis System (SAS) code:

- LowerCL = 1-betainv(1-alpha/2,N-x+1,x)
- UpperCL = betainv(1-alpha/2,x+1,N-x)

The number and percentage of p16 Immunohistochemistry (IHC) result (Positive, Negative), along with the 95% CI, was calculated using the Clopper-Pearson method by dose Cohort. Summary of shift from baseline of p16 IHC result by dose Cohort was also provided. Exploratory analyses of additional potential relevant markers such as PD-L1 status (programmed death ligand 1), FOXP3 (forkhead box P3), CD3, CD8 and T cell immunogenicity, etc. were performed for patients with available data.

Conization

For patients that underwent a conization procedure during the study, the date of conization was collected. The conization date collected and last visit prior to conization are listed. Conizations affect the efficacy and/or immunogenicity results in each Cohort. For affected efficacy and immunogenicity tables, the data for patients after conization is shown in a separate column. The conizated patients are flagged in related listings.

Exposure

Exposure and compliance were summarized for VB10.16 by dose Cohort using descriptive statistics (counts and percentages; mean, median, standard deviation, minimum, maximum).

Selection of vaccination schedule for Expansion Phase

Based on the Cohort Review Committee (CRC), interim analysis of the safety, immunogenicity and clinical outcome data from the 16 women enrolled in the parallel dosing schedules (Cohorts 1 and 2) at Visit 5 (Week 16), the dosing schedule with shorter vaccination intervals (Cohort 1) was selected for the subsequent Expansion Phase of the study. The selection was based on the decision criteria outlined in the report and the following summary results:

- Safety data showed no difference in the safety profile between the 2 Cohorts. No SAEs were observed in any of the patients treated and all related AEs were mild to moderate, the majority being local administration site reactions.
- Immunogenicity data were available for 14 patients, 7 in each Cohort. In Cohort 1, 6 of the 7 patients and in Cohort 2 all 7 patients, demonstrated a clear increase in HPV16 specific peripheral T cell response. The responses of the patients treated with the shorter intervals, were faster, stronger and longer lasting.
- Early signs of efficacy correlating with the immune responses could be observed in the patients (CIN regression to CIN 1 or no CIN, HPV clearance and p16 negativity).

Overall summaries

Demographics summary

A total of 38 female patients were screened in the study. Thirty-four of these were included in the safety evaluable population. The median age of these 34 patients was 29.0 years (range: 24 to 46 years) and all patients were white (100%). Twenty-four patients (70.6%) had CIN 2 and 10 patients (29.4%) had CIN 3. Thirty-three patients (97.1%) were positive for HPV16 and no patients were positive for HPV18. Fifteen patients (44.1%) tested positive for other high risk HPV strains. All patients had an ECOG performance status of 0 at the time of enrollment.

Safety summary

Thirty-four patients were treated with VB10.16 and evaluated for safety. Sixteen patients (47.1%) in Cohort 1 and 2 received 3 vaccinations. Seventeen patients (50.0%) in the Expansion Cohort received 4 vaccinations and 1 patient (2.9%) received 2 vaccinations before treatment was stopped, due to retrospectively determined screen failure (not positive HPV16). VB10.16 was well tolerated. No patients experienced SAEs, discontinued the study vaccine, experienced a DLT, or died within 30 days of receiving study drug. The AEs were generally evenly distributed across the Cohorts. The most common drug-related AEs were related to the injections: injection site pain (27 patients, 79.4%), injection site erythema (17 patients, 50.0%), injection site hypersensitivity (14 patients, 41.2%), injection site hyperesthesia (13 patients, 38.2%), The injection site events were solicited through the use of a patient diary and expected with the mode of administration. In general (81%), injection site events resolved within 4 days and were mild in nature, with 99% of events as Grade 1 or 2. Most AEs occurred as TEAEs within day 1 to 30 days post last dose. The highest Grade AEs were Grade 3, experienced by 3 patients. Two patients experienced 3 Grade 3 TEAEs, from day 1 to 30 days post last dose and 1 patient experienced Grade 3 LEAEs, after Week 24.

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Efficacy summary

Thirty-four patients were treated with VB10.16 and 33 patients (97.1%) were evaluated for efficacy. Patients in cohort 1 and 2 received 3 vaccinations at different time-regimen to decide the optimal vaccination schedule to be used in the expansion cohort – see Immunogenicity summary below.

The Expansion Phase enrolled 18 CIN 2 / CIN 3 patients, 1 patient (5.6%) was not HPV16 positive and thus 17 patients (4.4%) received 4 doses of 3 mg VB10.16 at Week 0, 3, 6 and 16. Two patients (11.8%) had conizations and 1 patient (5.8%) withdrew after 9 months and could not be assessed at Visit 8 (Month 12). Of the remaining 14 patients (82.4%), 12 patients (70.6%) showed a reduction in the lesion size; 8 patients (47.1%) had more than a 50% reduction in lesion size. Presence of HPV16 was evaluated from immunohistochemistry (p16) and Cobas® HPV test (Roche diagnostics). All patients (100%) had positive HPV16 at study entry and 8 of the 14 patients (57.1%) had negative HPV16 in 1 or both of the 2 tests at Visit 8 (Month 12), indicating clearance of the HPV16 infection. All patients were p16 positive at study entry and 6 of the 14 patients (42.8%) experienced overall p16 clearance by Visit 8 (Month 12). Histopathological regression to low grade neoplasia (CIN 1) or no CIN was seen in 8 patients.

All patients achieved a disease control response within the study, but some patients did not show a lasting response to VB10.16.

Immunogenicity summary

Thirty-four patients were treated with VB10.16 and 33 patients (97.1%) were evaluated for immunogenicity. For Cohorts 1 and 2 combined and after vaccination, a HPV16 specific T cell response was elicited in 13 out of 14 patients (92.9%). T cell immunogenicity responses of patients treated within shorter intervals (Cohort 1) were faster, stronger and longer lasting than the response of patients treated within longer intervals (Cohort 2). Therefore, the shorter interval dosing schedule used in Cohort 1 was used for the Expansion Cohort in addition to a boosting dose at Visit 5 (Week 16). The Expansion Cohort benefited from an increase in the number of vaccinations, from 3 to 4, and observed a boosting effect from the fourth vaccination resulting in the strongest average immune response observed at Visit 6 (Week 24), the latest measurement. Seventeen patients (100%) in the Expansion Cohort elicited a HPV16 specific T cell response where 16 (94.1%) showed an increased response after vaccination. Signs of efficacy (CIN regression, $HPV16^+$ clearance and lesion size reduction) correlating with the immune responses could be observed in the patients. In patients who did not show signs of efficacy (CIN regression, HPV16 clearance and lesion size reduction), an upreguation of PD-L1 was observed which could have inhibited the T cells response induced by the vaccine.

Summary conclusions

VB10.16 was administered to 2 different Cohorts, each following a different schedule of 3 vaccinations. Cohort 1 followed shorter intervals than Cohort 2. After preliminary results in safety, efficacy and immunogenicity were compared for these Cohorts, the short interval schedule of Cohort 1 was chosen for the Expansion Cohort. The Expansion Cohort also benefited from a fourth vaccination which resulted in a boosting effect from the fourth vaccination and the strongest average immune response was observed at Visit 6 (Week 24).

The primary objective of the study, to assess the safety/tolerability of 3 mg VB10.16 immunotherapy in patients with $HPV16^+$ CIN 2/3, was completed. The treatment with 4 doses of VB10.16 was well tolerated. The most frequently reported AEs were transient mild to moderate reactions at the injection site.. No patients experienced SAEs, discontinued the study vaccine, experienced a DLT, or died within 30 days of receiving study drug. The highest Grade AEs were Grade 3, experienced by 3 patients. Two patients experienced 3 Grade 3 TEAEs, from day 1 to 30 days post last dose and 1 patient experienced Grade 3 LEAEs, after Week 24.

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The secondary objectives for efficacy and immunogenicity were completed. In the Expansion Cohort immunological analyses of the peripheral T cell responses demonstrated a strong HPV16-specific T cell immune response in 17 of 17 patients (100%). An initial correlation between efficacy and immunogenicity results was observed.
These results constitute a proof-of-concept for VB10.16 and the Vaccibody DNA vaccine technology delivered by PharmaJet® Stratis 0.5 mL needle-free injection system. The treatment induced rapid, strong and long-lasting immune responses, was well tolerated and showed early signs of clinical effect.