Amsterdam, 22 July 2021
EMA/CHMP/576523/2021
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Oportuzumab monatox DLRC Pharma Services

International non-proprietary name: oportuzumab monatox

Procedure No. EMEA/H/C/005730/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of Contents

List of abbreviations

ADA	Anti-drug antibody
AEs	Adverse events
AET	Analytical evaluation threshold
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
AUA	American Urology Association
BCG	Bacillus Calmette-Guérin
BIW	Twice weekly
BLA	Biologics License Application
BPOG	BioPhorum Operations Group
CCS	Container closure system
CIS	Carcinoma *in situ*
CI	Confidence interval
CPA	Critical process attribute
CPP	Critical process parameter
CQA	Critical quality attribute
CR	Complete response
CSR	Clinical study report
DAMPs	Damage-Associated Molecular Patterns
DLTs	Dose limiting toxicity
DP	Drug Product
DoR	Duration of response
DS	Drug Substance
ECG	Electrocardiogram
EFS	Event-free survival
ELISA	Enzyme linked immunosorbent assay
EP	European Pharmacopoeia
EpCAM	Epithelial cell adhesion molecule
ETA	Pseudomonas Exotoxin A
FDA	Food and Drug Administration
FMEA	Failure modes and effects analysis

GMP	Good Manufacturing Practice
HCP	Host cell proteins
IHC	Immunohistochemistry
IPC	In-process controls
KPA	Key process attribute
KPP	Key process parameter
LDPE	Low-density polyethylene
LER	Low endotoxin recovery
LTFU	Long term follow-up
LLOQ	Lower Limit of Quantification
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MIBC	Muscle invasive bladder cancer
mITT	Modified intent-to-treat
MTS	3-[4,5,dimethylthiazol-2-yl]-5-[3-carboxymethoxy-phenyl]-2-[4- sulfophenyl]-2H- tetrazolium salt
NA	Not analysable
NMIBC	Non-muscle invasive bladder cancer
OBS	Orthotopic bladder substitute
OC	Other concern
OOS	Out of specification
OS	Overall survival
PACMP	Post-approval change management protocol
PBS	Phosphate-buffered saline
PDE	Permitted daily exposure
PFS	Progression-free survival
PK	Pharmacokinetics
PPQ	Process performance qualification
QTTP	Quality Target Product Profile
RF	Recurrence-free
SAE	Serious adverse event
SAP	Statistical analysis plan
SCCHN	Squamous cell carcinoma of head and neck
scFv	Single-chain variable fragment
sCR	Sustained complete response

SE	Standard error
SPC	Summary of (medicinal) Product Characteristics
TCC	Transitional cell carcinoma
TEAEs	Treatment-emergent adverse events
TURBT	Transurethral resection of bladder tumour
UF/DF	Ultrafiltration/diafiltration
USP	United States Pharmacopoiea
VLS	Vascular leak syndrome
WCB	Working cell bank

1. Recommendations

Based on the review of the data on quality, safety, efficacy, the application for Oportuzumab monatox in

- the treatment and prevention of recurrence of carcinoma-in-situ (CIS) of the urinary bladder following transurethral resection in BCG-unresponsive patients.
- the prevention of recurrence of high grade Ta and/or T1 papillary tumours following transurethral resection in BCG-unresponsive patients.

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the List of Questions (removed from this report).

In addition, satisfactory answers must be given to the "other concerns" as detailed in the List of Questions (removed from this report).

The major objections precluding a recommendation of marketing authorisation, pertain to the following principal deficiencies:

- **Quality:**

  Potency: Seven different processes were used during the clinical development and the comparability with regard to potency is not considered sufficiently explained and has resulted in several questions.

  A nitrosamine risk assessment is pending.

  Proof of GMP compliance should be provided for the proposed drug substance manufacture and QC testing site.

- **GCP:**

  GCP inspection proposed. Major concerns have emerged regarding the conduct of the pivotal study and the reliability of the database.

- **Efficacy:**

  Wording of indication does not reflect the study population.

  Expected effect size.

  Pivotal study not controlled for multiplicity.

  Primary endpoint changed while the study was ongoing and the use of complete response (CR) at 3 month as primary endpoint.

  Clinical relevance of the primary endpoint.

  Justification of the chosen follow-up time and request for updated data.

  Justification of all-comers indication.

- **Safety:**

  Concerns about systemic exposure.

Questions to be posed to additional experts

Not applicable.

Inspection issues

GMP inspection

GMP audit of the cell bank storage/testing site was last performed in February 2015, with a complementary HPRA audit performed in December 2019. An additional audit is scheduled in April 2021, with anticipated report and close-out during the period of MAA assessment. Due to COVID-19 restrictions, this will be a remote audit in the first instance, with an onsite audit at the earliest opportunity thereafter; the QP declaration will be replaced at that point. The renewed QP-declaration should be provided.

A valid proof of GMP compliance should be provided for the proposed drug substance manufacture and QC testing site.

GCP inspection(s)

A request for GCP inspection is required for the following clinical study; VB4-845-02-IIIA. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day 121.

New active substance status

Based on the review of the data on the primary structure and mechanism of action the CHMP considers that the active substance oportuzumab monatox fusion protein (VB4-845) contained in the medicinal product oportuzumab monatox is considered to be qualified as a new active substance in itself.

2. Executive summary

2.1. Problem statement

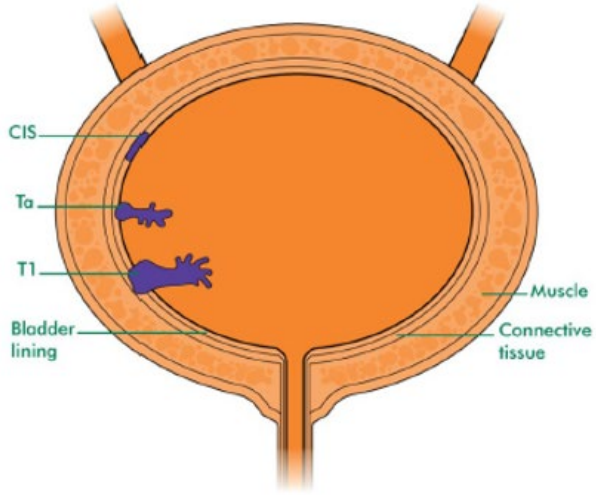
2.1.1. Disease or condition

Bladder cancer is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to eleventh when both genders are considered (EAU). Bladder cancer is a general term for several types of malignant tumours of the urinary bladder. NMIBC, or previous referred to as "superficial" bladder cancer, accounts for approximately 75-85% of bladder cancer, and is either confined to the mucosa (Stage Ta, CIS) or submucosa (Stage T1) (Anastastiadis et al., 2012; Woldu et al., 2017; Sanli and Lotan, 2017; Isharwal and Konety, 2015). Approximately 70% of NMIBC cases present as stage Ta, 20% as T1 and 10% as CIS (Anastastiadis et al., 2012).

NMIBC corresponds to disease that is confined to the mucosa and submucosa of the bladder and accounts for CIS and Stages Ta and T1 bladder cancers (Figure 1). Most tumours found in the bladder are low-grade, and these tumours are known to have low progression rates and, therefore, a good prognosis. High-grade bladder tumours are associated with high malignant potential associated with

significant progression, resulting in poor prognosis and increased mortality (Epstein et al., 2010; Ranasinghe 2013; Pasin et al., 2008).

Figure 1: Stages of Non-Muscle Invasive Bladder Cancer (MacMillan, 2019)



CIS, representing approximately 10% of NMIBC, is characterised by severe cellular dysplasia in the absence of discrete tumour formation and is associated with a high incidence of subsequent progression to muscle invasive bladder cancer (MIBC) in 60-80% of patients.

Stage Ta tumours are confined to the urothelium, have a papillary morphology and do not penetrate into the underlying tissues. The majority of these tumours are considered low grade with 2-18% considered high-grade. Recurrence with these tumours is high, and high-grade Ta tumours have a high risk of invasion in the lamina propria (40%) and surrounding muscle (25%).

T1 tumours form in the urothelium and are tumours that have penetrated into the basement membrane (lamina propria) but have not reached the detrusor muscle. These tumours are usually papillary; a nodular or sessile appearance suggests deeper invasion compared to Ta and the majority (71%) are considered high-grade. High-grade T1 tumours grow rapidly, have a high potential for recurrence and progression to invasion, metastasis and death.

The claimed indications in this application is NMIBC.

2.1.2. Epidemiology and risk factors, screening tools/prevention

In the European Union (EU-28), according to the estimates of the International Agency for Research on Cancer (IARC), bladder cancer ranks fifth among the most frequently diagnosed cancers with about 124,000 new cases (men: 97,000; women: 27,000) predicted in 2012 for both sexes and it is expected to grow up to 141,000 in 2020 (US: about 80,000), representing around 5% of all the incident cases.

The epidemiology of bladder cancer is strictly related to that of its main risk factor: smoking. Therefore, the temporal trend of age standardised incidence rates has followed the changes in the prevalence of smokers of the populations. Indeed, in many countries there was a long-standing increasing tendency (especially among men) in the past years, followed by a more recent decrease and/or a flattening of trends. As regards cancer mortality, in European Union bladder cancer represents the ninth cause of death, with around 40,000 deaths (3% of all the total cancer deaths) estimated in 2012 and nearly 43,000 estimated for 2015. Mortality for bladder cancer decreases over

time throughout in Europe among men, while it is stable or decreases among women. The most recent data of the Eurocare project (Eurocare-5) showed that the 5-year relative survival for bladder cancers diagnosed in 2000-2007 is on average around 69% (Marcos-Gracera et al. Eur J Cancer 2015), varying from 75% in Northern to 65% in Eastern Europe. Some of the differences are presumably related to the stage at diagnosis. In fact, after one year since diagnosis the probability to survive additional 5 years not only improves substantially – it is on average 81%. Finally, and differently from many other tumours, bladder cancer survival is higher for men (European age-standardised 5-year relative survival 69%) than for women (66%) (The European Commission's science and knowledge service).

Management of bladder cancer is based on the findings of the biopsy and TURBT specimens, with attention to histology, grade, and depth of invasion. These factors are used to estimate the probability of recurrence and progression to a more advanced stage. Patient bladder function, comorbidities, and life expectancy are also important considerations.

NMIBC is a heterogeneous disease associated with high rates of recurrence that requires more than 5 years of surveillance and in some cases lifelong. For over 30 years, the treatment for NMIBC (CIS, Ta and T1) has been transurethral resection of bladder tumour (TURBT) in conjunction with intravesical BCG immunotherapy. However, 30% of patients never respond to BCG, while 30-70% of the remainder eventually develop recurrent tumours.

2.1.3. Aetiology and pathogenesis

Risk factors for developing bladder cancer include male sex, white race, smoking, personal or family history of bladder cancer, pelvic radiation, environmental/occupational exposures, exposure to certain drugs, chronic infection or irritation of the urinary tract, and certain medical conditions including obesity and diabetes. Although diabetes mellitus appears to be associated with an elevated risk of developing bladder cancer, treatment with metformin may be associated with improved prognosis in patients with bladder cancer and diabetes. Certain genetic syndromes, most notably Lynch syndrome, may also predispose an individual to urothelial carcinoma.

As mentioned the main risk factor is smoking and the pathogenesis is poorly understood.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

The most common presenting symptom in patients with bladder cancer is microscopic or gross haematuria, although urinary frequency due to irritation or a reduced bladder capacity can also develop. Less commonly, the presenting symptom is a urinary tract infection. Upper tract obstruction or pain may occur in patients with a more advanced lesion. Patients presenting with these symptoms should be evaluated with office cystoscopy to determine if a lesion is present. If one is documented, the patient should be scheduled for a transurethral resection of the bladder tumour (TURBT) to confirm the diagnosis and determine the extent of disease within the bladder. Urine cytology may also be obtained around the time of cystoscopy. Positive urinary cytology may indicate urothelial tumour anywhere in the urinary tract. In the presence of a positive cytology and a normal cystoscopy, the upper tracts and the prostate (prostatic urethra) in men must be evaluated and ureteroscopy may be considered. Clinical investigation of the specimen obtained by TURBT or biopsies is an important step in the diagnosis and subsequent management of bladder cancer. The modifier "c" before the stage refers to clinical staging based on bimanual examination under anaesthesia, endoscopic surgery (biopsy or TURBT), and imaging studies. A modifier "p" would refer to pathologic staging based on cystectomy and lymph node dissection.

Papillary tumours confined to the mucosa or submucosa are generally managed endoscopically with complete resection. Progression to a more advanced stage may result in local symptoms or, less commonly, symptoms related to metastatic disease. An estimated 31%–78% of patients with a tumour confined to the mucosa or submucosa will experience a recurrence or new occurrence of urothelial carcinoma within 5 years. These probabilities of recurrence vary as a function of the initial stage and grade, size, and multiplicity. Refining these estimates for individual patients is an area of active research.

2.1.5. Management

NMIBC

The NCCN Guidelines for Bladder Cancer generally manage NMIBC with intravesical therapy or, for those at particularly high risk, cystectomy.

Intravesical Therapy

Intravesical therapy is implemented to reduce recurrence or delay progression of bladder cancer to a higher grade or stage.

Immediate Intravesical Therapy Post TURBT

An immediate intravesical instillation of chemotherapy may be given within 24 hours of TURBT to prevent tumour cell implantation and early recurrence. Immediate intravesical chemotherapy has been shown to decrease recurrence in select subgroups of patients. A systematic review and meta-analysis of 13 randomised trials showed a decreased risk of recurrence by 35% and a decreased 5-year recurrence rate from 58.8% to 44.8% when comparing immediate intravesical chemotherapy after TURBT to TURBT alone, although the instillation did not prolong the time to progression or time to death from bladder cancer. This study also found that the instillation did not reduce recurrences in patients who had a prior recurrence rate of >1 recurrence per year.

Phase III trials have reported a reduced risk of recurrence for patients with suspected NMIBC who are treated with immediate postoperative gemcitabine or mitomycin. A randomised, double-blind, phase III trial of 406 patients with suspected low-grade NMIBC based on cystoscopic appearance showed that immediate post-TURBT instillation of gemcitabine reduced the rate of recurrence compared with saline instillation (placebo). Another phase III, prospective, multicentre, randomised study of 2,844 patients with NMIBC showed that an immediate instillation of mitomycin C after TURBT reduces recurrence regardless of the number of adjuvant instillations.

Gemcitabine is preferred over mitomycin based on toxicity profiles and lower cost. For tumours with an intermediate or high risk of progression, subsequent treatment with intravesical induction (adjuvant) therapy may be given.

Induction (Adjuvant) Intravesical Chemotherapy or BCG

Although only intravesical chemotherapy is recommended in the immediate postoperative setting, both intravesical chemotherapy and BCG have been given as induction therapy in patients with NMIBC.

Induction BCG has been shown to decrease the risk of bladder cancer recurrences after TURBT. BCG therapy is commonly given once a week for 6 weeks, followed by a rest period of 4 to 6 weeks, with a full re-evaluation at week 12 (ie, 3 months) after the start of therapy.

BCG has also been compared with gemcitabine and epirubicin. The benefit of BCG with or without isoniazid compared with epirubicin alone in a long-term study of 957 patients with intermediate- or

high-risk Ta or T1 disease was measured by a reduced recurrence, greater time to distant metastases, and greater overall survival (OS) and disease-specific survival (DSS); progression was similar. Patients in the studies received 2 to 3 years of maintenance therapy.

Maintenance Therapy

Maintenance intravesical therapy may be considered after induction with chemotherapy or BCG. The role of maintenance chemotherapy is controversial. When given, maintenance chemotherapy is generally monthly. The role of maintenance BCG in those patients with intermediate to high-risk NMIBC is more established, although the exact regimens have varied across studies. Most patients receive maintenance BCG for 1 to 3 years. A study of 1,355 patients with a median follow-up of 7.1 years found no benefit in 3 years of maintenance BCG compared with 1 year for intermediate-risk patients. Conversely, 3-year maintenance BCG reduced recurrence compared with 1-year maintenance but did not impact progression or survival in high-risk patients. These data suggest that 1 year may be suitable for patients at intermediate risk whereas 3 years of maintenance is preferred for high-risk disease. It should also be noted that duration of treatment may be limited by toxicity and patient refusal to continue.

For patients showing no residual disease at follow-up cystoscopy, whether 1 or 2 courses of induction therapy were administered, maintenance therapy with BCG is preferred. This recommendation is based on findings that an induction course of intravesical therapy followed by a maintenance regimen produced better outcomes than intravesical chemotherapy.

There are concerns regarding potentially severe local and systemic side effects and the inconsistent availability of BCG. BCG induces a systemic nonspecific immunostimulatory response leading to secretion of proinflammatory cytokines. This causes patients to experience flu-like symptoms that may last 48 to 72 hours. Installation of BCG into the bladder also mimics a urinary tract infection and may produce intense local discomfort.

Pembrolizumab for NMIBC

Pembrolizumab is a PD-1 inhibitor that has been evaluated as treatment of BCG-unresponsive, NMIBC with CIS in the single-arm, phase II KEYNOTE-057 study, reported to date in abstract form (pembrolizumab is also indicated for treatment of metastatic urothelial carcinoma, for the metastatic setting). In the KEYNOTE-057 study, 103 patients with high-risk CIS, with or without papillary tumour, who received previous BCG therapy and were either unable or unwilling to undergo cystectomy were treated with pembrolizumab. The 3-month complete response rate was 38.8% (95% CI, 29.4%–48.9%), with 72.5% of complete responses maintained at last follow-up (median 14.0 months). Therefore, of the total study population, 28% had a complete response at the time of last follow-up. The median duration of complete response had not yet been reached at the time of analysis. Clinical data included in the package insert for 96 patients on this trial report a complete response rate of 41% (95% CI, 31%–51%) and a median duration of response (DOR) of 16.2 months with 46% of complete responses maintained for at least a year. This study is followed up with a Phase 3 trial investigating reinduction with BCG +/- pembrolizumab.

Treatment of cTa, High-Grade Tumours

Tumours staged as cTa, high-grade lesions are papillary tumours with a relatively high risk for recurrence and progression toward more invasiveness. Repeat resection is recommended if there is incomplete resection, or should be strongly considered if there is no muscle in the specimen. After TURBT, patients with cTa, high-grade tumours may be treated with intravesical BCG (preferred), intravesical chemotherapy, or observation. The NCCN Bladder Cancer Panel Members recommend BCG

as the preferred option over intravesical chemotherapy for adjuvant treatment of high-grade lesions, followed by maintenance therapy according to risk and availability of intravesical agents.

Treatment of cT1 Tumours

Based on the histologic differentiation, most cT1 lesions are high grade and considered to be potentially dangerous, with a higher risk for recurrence and progression. These tumours may occur as solitary lesions or as multifocal tumours with or without an associated Cis component. These tumours are treated with a complete endoscopic resection, and repeat TURBT is strongly advised. If residual cT1 disease is found at repeat TURBT, treatment should consist of BCG (category 1) or cystectomy. If no residual disease is found after the second resection, intravesical therapy with BCG (preferred; category 1) or intravesical chemotherapy is recommended.

Recurrence After Intravesical Treatment

In a phase II multicentre study of NMIBC that recurred after 2 courses of BCG, intravesical gemcitabine demonstrated activity that was relegated to high-risk NMIBC. In the 47 patients with evaluable response, 47% had disease-free survival at 3 months. The 1-year relapse-free survival (RFS) was 28% with all cases except for 2 attributed to the high-risk group. The 2-year RFS was 21%. Intravesical gemcitabine had some activity in the high-risk group and may be an option if a candidate is not eligible for a cystectomy; however, the study results indicate that cystectomy is preferred when possible. Similarly, for patients with recurrence of high-grade cT1 disease after TURBT and induction BCG, cystectomy is the recommended option with the best data for cure, although pembrolizumab may be appropriate for patients with BCG-unresponsive, high-risk, NMIBC with CIS, with or without papillary tumours, who are ineligible for or have elected not to undergo cystectomy. The data are currently not mature enough to determine if pembrolizumab can be considered curative in this setting.

After the initial intravesical treatment and 12-week evaluation, patients with persistent cTa, cT1, or Cis disease tumours can be given a second induction course of induction therapy. No more than 2 consecutive induction courses should be given. If a second course is given, TURBT is performed to determine the presence of residual disease at the second 12-week follow-up. If no residual disease is found, maintenance BCG is recommended for patients who received prior BCG.

If residual disease is seen after TURBT, patients with persistent cT1 tumours are recommended to proceed to cystectomy. Nonsurgical candidates can consider concurrent chemoradiation, change of the intravesical agent, or a clinical trial. Patients with persistent Cis or cTa disease after TURBT may be treated with a different intravesical agent, cystectomy, or pembrolizumab if Cis is present and the patient is not a candidate for cystectomy. Concurrent chemoradiotherapy can be considered for non-cystectomy candidates with persistent Ta or Cis disease after TURBT, although it is a category 2B recommendation for this setting. Valrubicin is approved for CIS that is refractory to BCG, although panelists disagree on its value. For patients with disease that does not respond or shows an incomplete response to treatment, subsequent management is cystectomy.

Unmet medical need

It is acknowledged that there is a need for bladder-sparing therapy as the standard treatment is RC in subjects experiencing recurrent NMIBC after failing sufficient treatment with BCG and taking into account that only 10% of subjects with NIMBC progress to a more advanced stage of the disease with metastases. This need though is more pronounced for patients not eligible for or not willing to undergo RC. Further, retrospective studies have showed that patients who developed a NMIBC recurrence had similar OS and disease-specific survival (DSS) to those who did not. Twenty-four % of CRs developed a

NMIBC recurrence after combined-modality therapy (CMT) after mean follow-up of 5.1 years. It seems that thorough surveillance and control in selected cases can be used safely.

2.2. About the product

VB4-845 is a novel pharmacologic class that specifically binds to EpCAM, a cell-surface antigen overexpressed on a wide variety of epithelial-derived cancer cells including urothelial carcinomas that have been shown to overexpress EpCAM with limited expression on normal epithelium. The specific binding of EpCAM on urothelial cancers by VB4-845 preferentially targets and kills these cancer cells while sparing normal urothelium.

VB4-845 has a dual mechanism of action that consists of a well-defined, antibody-directed cytotoxic effect that promotes a cell-mediated, anti-tumour immune response. The first mechanism involves ETA-induced cytotoxicity resulting from inhibition of protein synthesis. This killing mechanism is effective against both rapidly proliferating cancer cells as well as slowly dividing or quiescent cancer stem-like cells and is not susceptible to multidrug resistance. EpCAM binding must occur in order for ETA (252-608) to mediate its cytotoxic effect. Once bound, VB4-845 is internalised through an endocytic pathway. Furin within the endosomal compartment cleaves a proteolytic site within ETA (252-608), releasing ETA (280- 608). ETA (280-608) induces cell death by irreversibly blocking protein synthesis through adenosine diphosphate (ADP)-ribosylation of a post-translationally modified histidine residue of elongation factor-2 (EF-2), called diphthamide (Oppenheimer and Bodley, 1981). The second mechanism is believed to involve the promotion of a cell-mediated anti-tumour immune response subsequent to the appearance of immunogenic cell death (ICD) biomarkers, also referred to a damage-associated molecular patterns or DAMPs, elicited during direct VB4-845 tumour cell killing. The release of tumour neoantigens and the appearance of DAMPs are believed to facilitate a T cell-mediated anti-tumour response.

2.3. The development programme/compliance with CHMP guidance/scientific advice

This clinical overview provides a critical analysis of the clinical data in the VB4-845 MAA. These data come from 243 subjects exposed to VB4-845 for periods up to 782 days in clinical trials.

The efficacy and safety of intravesical VB4-845 have been studied in subjects with an established diagnosis of NMIBC CIS and high-grade papillary disease of the bladder that were previously treated with BCG. The primary efficacy analysis was derived from a single Phase 3 study with Phase 2 and Phase 1/2 studies providing supporting evidence.

The Phase 1/2 study was an open-label, multicentre, dose escalating study of VB4-845 administered to subjects with BCG refractory or intolerant urothelial carcinoma of the bladder, with doses up to 30.16 mg.

The Phase 2 study was a single treatment arm, dual-treatment schedule, open label, non-randomized study in subjects with EpCAM-positive, non-invasive urothelial CIS with or without non-invasive papillary disease, who failed or were intolerant to previous treatment with BCG therapy. Two different induction strategies were used in the Phase 2 study. Subjects in Treatment Schedule A (Cohort 1) received an induction phase of 30 mg once weekly for 6 weeks, followed by 6 weeks of no therapy. Subjects in Cohort 1 who had residual disease (<T2) after induction were permitted to proceed to maintenance or have a second induction course. Subjects in Treatment Schedule B (Cohort 2) received an induction phase consisting of 30 mg once weekly for 12 weeks.

The Phase 3 study is an open-label, non-randomised, multicentre study in subjects with BCG-unresponsive NMIBC. In this study, during the induction phase, subjects received 30 mg of VB4-845 twice a week (BIW) for 6 weeks followed by once weekly for 6 weeks. Although both the Phase 2 and Phase 3 studies used a 30 mg dose of VB4-845, a different dosing regimen was used across the two studies to evaluate the effectiveness to control the disease in subjects with NMIBC. A total of 18 doses were administered with the dosing regimen used in the Phase 3 study as opposed to the 12 doses used in Cohort 2 of the Phase 2 study.

As of October 06, 2020, 24-month data was available for all subjects in the Phase 3 study VB4-845-02-IIIA. Following the last dose of study drug, there is a protocol specified post-treatment follow-up period of 2 years. The last subject received their final dose of study drug in study VB4-845-02-IIIA on April 24, 2020 and therefore the anticipated completion of the study will be in April 2022.

Scientific advice

The applicant requested scientific advice for the first time on 29 May 2009 where CHMP commended that the pivotal phase III trial designed as a single-arm trial might be useful to gain insight in the effect size of Oportuzumab. If of uncontrolled design, the trial (A) is **not** considered adequate to support conditional/full MA, and at the discussion meeting it was agreed that the inclusion of a comparator arm would be a better use of resources. This would be followed by a second confirmatory phase III trial (B) designed as a randomised controlled trial vs. a reference product. In conclusion, the Applicant is advised to proceed to the randomised controlled trial based on the phase II results available and not to divert patients into an uncontrolled trial that is likely to be at most only supportive. The next scientific advice was held on 17 January 2020 on a time point where enrolment of the pivotal phase 3 study was apparently complete and preliminary results were available. This limits the potential impact of an advice at such a late stage. Considering that the phase 3 study has already been conducted and the trial design cannot be amended, decisions on whether the existing clinical data will support the MAA will be made at the review of the application. Time-dependent endpoints such as e.g., EFS, PFS or OS being highly sensitive to prognostic factors and not only to tumoural response are much less reliable in the context of a single-arm trial. In this specific case, it should be justified that the proposed endpoint is able to isolate treatment effect in particular in the proposed CIS NMIBC population. Moreover, the clinical relevance of CR rate at 3 months is considered questionable; a cut off of CR at 6 months has a higher clinical relevance for efficacy evaluation, although an assessment of response at 3 months should be done to ascertain the need for surgery in case of progression.

The applicant received Scientific Advice on the development of Oportuzumab monatox from the CHMP on 28 May 2020. The Scientific Advice pertained to the following quality aspects:

- The proposed commercial test methods and characterisation for DS and DP release and stability specifications
- The proposed comparability approach following process changes for clinical trial material and the commercial manufacturing process
- The approach to characterising DP and DS stability and shelf-life
- The proposed validation strategy for the PPQ studies
- The proposed approach to establishing the overall control strategy
- Advice on the requirements for the wash buffer and its characterisation of residual levels in DS

Overall, the advice given has been followed by the applicant. However, the applicant was advised to characterise the charged variants to evaluate whether the specification proposed is appropriate, *i.e.* whether the various variants have similar behaviour with regard to the mechanism of action, safety

and efficacy compared to the predominant form. The characterisation of the charged variants is still pending and issues have been raised which should be resolved.

2.4. General comments on compliance with GMP, GLP, GCP

GMP

Active substance

Production of VB4-845 active substance, manufacture of the master cell bank and working cell bank, release and stability testing and primary storage of cell banks are performed by various sites in the USA.

Since US FDA does not issue GMP certificates, drug establishment current registration status for all drug substance manufacturing sites, published on the US FDA website, have been provided in Annex 5.9 of Module 1.

Qualified Person´s Declaration concerning GMP compliance of the active substance manufacturers is provided in Annex 5.22. According to the declaration, GMP audits have been performed for the manufacturers of the cell banks and active substance in February and July 2019 respectively.

GMP audit of the cell bank storage/testing site was last performed in February 2015, with a complementary HPRA audit performed in December 2019. An additional audit is scheduled in April 2021, with anticipated report and close-out during the period of MAA assessment. Due to COVID-19 restrictions, this will be a remote audit in the first instance, with an onsite audit at the earliest opportunity thereafter; the QP declaration will be replaced at that point. The renewed QP-declaration should be provided.

Finished product

VB4-845 drug product is manufactured at a site in Germany. Release and stability testing are performed by the same site, except testing for potency and flow cytometry which is performed by the active substance manufacturer. Secondary packaging is performed by a site in Ireland. A valid GMP certificate is found for the drug product manufacturing site. For the active substance site responsible for potency and flow cytometry, a QP declaration concerning GMP compliance is provided.

Diluent

A valid GMP certificate for the diluent testing site is requested.

GLP

Only two repeat-dose toxicity studies are presented to support this submission. Both appear to be conducted in compliance with GLP with internal quality assurance and audit programmes, however bioanalysis was not documented according to current standards. Since the studies were conducted more than 10 years ago and prior to issuing of current guidelines concerning bioanalysis and that toxicity and immunogenicity was observed in both studies, this will not trigger a GLP inspection.

GCP

The conduct of the pivotal study (and also the dose response studies as the matter of fact) with an original protocol as of 03 April 2015 has had a changeable existence with several amendments with substantial changes in the SAP and changes in the inclusion/exclusion criteria. However, it is difficult to assess if these SAP changes are of extensive importance as nothing about these changes are mentioned in the CSR. The recruiting progress, participant flow, baseline characteristics and numbers

analysed is not clear. Besides, while according to PK data systemic exposure appears negligible, the reported adverse events call this assumption into question. Further, the dossier is based on the results from a single pivotal trial. These uncertainties and concerns about the credibility of data should trigger a GCP inspection.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

PRIME

Not applicable.

Accelerated assessment

The applicant has requested accelerated assessment.

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. The applicant's request for an accelerated assessment has not been duly substantiated. The product is not expected to:

- impact medical practice
- change the natural history of the disease
- provide a therapeutic advantage compared to available treatments, survival benefit or other important benefit.

There is not a sufficiently large unmet need for the proposed population that would constitute a major public health need. Other treatment options, as mentioned previously, exist for these patients.

The single arm study is not considered strong evidence in this setting given that there is, e.g. surgical cure. The lack of detrimental effect on OS cannot be shown with this trial design. The clinical relevance of the 3-month timepoint for complete response compared to 6 months is not clearly justified. It will also be important to put the CR into perspective in terms of long-term outcomes for example compared with chemotherapy or radiotherapy, this could be very interesting.

It would have been possible to conduct a randomised trial with the comparator arm as physician's choice of intervention (chemotherapy, radiotherapy, surveillance).

Conditional marketing authorisation

Not applicable. The applicant has requested a full marketing authorisation.

Marketing authorisation under exceptional circumstances

Not applicable.

Additional data exclusivity/ marketing protection

Not applicable.

New active substance status

The applicant requested the active substance oportuzumab monatox contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Orphan designation

Not applicable.

Similarity with orphan medicinal products

The application did not contain a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

Derogation(s) from orphan market exclusivity

Not applicable.

Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0287/2020 on the granting of a (product-specific) waiver.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

VB4-845 (also referred to as oportuzumab monatox) is a novel, locally-administered, anti-cancer therapeutic developed by Sesen Bio for the intravesical treatment of Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC).

VB4-845 drug substance is a recombinant polypeptide fusion protein consisting of a humanised single-chain antibody fragment (scFv) specific for the cancer cell surface target EpCAM (epithelial cell adhesion molecule), genetically-linked to a truncated form of *Pseudomonas* exotoxin A lacking the cell-binding domain (ETA(252-608)). Upon binding to EpCAM, VB4-845 is internalised through an endocytic pathway. Within the endosomal compartment, furin cleaves a proteolytic site within ETA(252-608), releasing ETA(280-608). ETA(280-608) induces cell death by irreversibly blocking protein synthesis through adenosine diphosphate (ADP)-ribosylation of a post-translationally modified histidine residue of elongation factor-2 (EF-2).

VB4-845 has a dual mechanism of action that consists of a well-defined, antibody-directed cytotoxic effect (described above) that promotes a cell-mediated, anti-tumour immune response. The first mechanism involves cytotoxicity against both rapidly proliferating cancer cells as well as slowly dividing or quiescent cancer stem-like cells and is not susceptible to multi-drug resistance. The second mechanism is believed to involve an immune T cell-mediated anti-tumour response. Tumour cell killing by VB4-845 occurs via an immunogenic cell death process leading to the appearance of DAMPs (Damaged-Associated Molecular Patterns) and the release of tumour neoantigens. These tumour

neoantigens serve to activate T cells which can then seek out and specifically kill any remaining cancer cells.

VB4-845 drug substance (DS) is produced in *E. coli*, transformed with a plasmid encoding the VB4-845 fusion protein, using a fed-batch fermentation process with a five-column chromatographic purification process.

The drug product is a sterile liquid solution aseptically filled into Type I glass vials and stored at -20°C. It is intended for intravesical administration following dilution in sterile diluent (phosphate buffered saline), co-packaged with the VB4-845 DP vial.

Name:	VB4-845 / Oportuzumab monatox
Dosage form and strength:	30 mg in 50 mL of phosphate buffer saline administered as an intravesical instillation.
Procedure:	Centralised, EMEA/H/C/005730
Therapeutic class or indication:	Intravesical treatment of Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC)
Proposed dosage range:	30 mg in 50 mL of phosphate buffer saline administered as an intravesical instillation.

3.1.2. Active Substance

General Information

Oportuzumab monatox (INN) also designated VB4-845 (Company code) is a recombinant fusion protein of 647 amino acids consisting of a humanised scFv (single-chain variable fragment, *i.e.* a fusion protein of the variable regions from one heavy and one light chain) with specificity for the EpCAM (Epithelial cell adhesion molecule, CD326) protein fused to a truncated form of *Pseudomonas* exotoxin A (ETA). The EpCAM is a transmembrane protein, which is involved in many cellular functions, and is overexpressed on urothelial carcinoma cells as well as many other types of carcinoma. VB4-845 is expressed in *E. coli* as a single-chain protein without glycosylation.

Manufacture, process controls and characterisation

Description of manufacturing process and process controls

The following process steps are performed by sites in the USA:

- Manufacture and testing of VB4-845 active substance. During assessment, a major objection was raised concerning the lack of a valid proof of GMP compliance for the proposed drug substance manufacture and QC testing site.
- Manufacture of master cell bank and working cell bank.
- Release and stability testing and primary storage of cell banks. During assessement, a renewed QP-declaration and appropriate proof of GMP compliance were requested for the release and stability testing and primary storage of cell banks site.

VB4-845 drug substance is produced in a recombinant *E. coli* cell line by fed-batch fermentation followed by purification of the drug substance from the culture supernatant by a number of filtration chromatography steps. The manufacturing process is considered standard. The upstream process consists of inoculum expansion in shake flasks. Inoculum expansion is followed by three phases of

cultivation in a fermentor: initial growth phase, fed-batch growth phase, and fed-batch induction phase. At the end of fermentation, the culture broth is harvested by centrifugation, followed by clarification by microfiltration and concentration by ultrafiltration/diafiltration. VB4-845 drug substance is purified via five chromatographic steps: Anion exchange chromatography (AEX), Nickel Affinity Chromatography (AFF), AEX2, Ceramic Hydroxyapatite Chromatography (CHT), and AEX3. The final AEX Eluate is formulated with polysorbate 80 (PS-80) and finally ultrafiltered/diafiltered (UF/DF) to achieve the final formulation (sodium phosphate, pH 8.0, PS-80) and concentration (5.0 g/L). The formulated VB4-845 drug substance is 0.45 µm/0.2 µm filtered into 10 L low density polyethylene (LDPE) bulk bags and stored at -20°C ± 5°C. Refiltration of bulk drug substance due to post-use filter integrity test failure according to a pre-approved protocol is allowed. No prolonged holding times are proposed. Drug substance is shipped to the drug product manufacturer in a validated, temperature-controlled shipper.

The drug substance batch scale is properly defined. Batch numbering is described in sufficient detail, and allows adequate identification and appropriate traceability of drug substance batches.

Overall, the manufacturing process is considered adequately described, however, some other concerns are posed on the manufacturing process.

The control strategy for the VB4-845 drug substance manufacturing process was established in line with ICH Q8 and ICH Q11 guidance. Relevant process parameters and in-process controls (IPC) including acceptance criteria/ranges are defined for the manufacturing process based on the defined quality target product profile and critical quality attributes, process characterisation, and criticality assessment of process parameters and attributes, and historical manufacturing process knowledge. A failure modes and effects analysis (FMEA) was conducted for parameter criticality assessment. Overall, the limits for the process are considered justified during drug substance process characterisation, and they are confirmed by the process validation; however, justification of the sufficiency of the proposed IPCs to control the quality of the chromatography columns, as well as provision of acceptance criteria, is requested.

Overall, the manufacturing process is considered adequately described and the applied process parameters and IPCs, well as their ranges, and the control of starting materials are considered adequate to control the process and ensure formation of drug substance of adequate and consistent quality. However, a few points need to be addressed concerning the proposed acceptable ranges for some output parameters.

Raw materials

Appropriate systems are in place for ensuring the suitability of raw materials. The raw materials are purchased against an approved specification from qualified vendors, the CoA reviewed, and each incoming raw material is tested for appearance and at least one specific identification test prior to use in the manufacturing process. Specifications have been included for all non-compendial raw materials, including filters, membranes, and resins.

Two biologically sourced raw materials are used in manufacture of the master and working cell banks (MCB and WCB). One material is of animal origin and meets the requirements of the EMA/410/01 rev. 3: *"Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via human and Veterinary Medicinal Products, Revision 3"*.

All media are sterilised by autoclaving and all product contact buffers and feeds are sterile filtered prior to use, with filter integrity test performed after filtration.

Cell banks

The structure and derivation of the plasmid construct and the host cell line, *E. coli* strain E104, is described. The production cell line was used to generate the first master cell bank from which the two first working cell banks, used for non-clinical and clinical Phase 1 and 2, were produced.

The MCB and WCBs were characterised according to the ICH Q5D guideline, addressing microbial purity, host cell identity, absence of bacteriophages, sequence identity of promoter and insert, identity of expressed protein, and plasmid copy number/cell.

Prior to phase 3, the sequence of the VB4-845 insert was codon optimised for increased fermentation yield, with no changes in the amino acid sequence of the VB4-845 protein. No significant changes in quality attributes were observed as a result of the codon optimisation of VB4-845 as observed from the comparability studies conducted accordingly.

A new master cell bank and working cell banks were generated from *E. coli* E104 competent cells transformed with the optimised expression construct. All cell banks for phase 3 and commercial manufacture were generated under cGMP and have been characterised according to ICH Q5D, overall, demonstrating that they are suitable for their purpose. However, minor issues have been identified in relation to Western Blot data for protein expression at cell bank level and need to be further justified.

Adequate description of determination of limit of *in vitro* cell age, verification of cell bank stability, and protocols for generation and qualification of future cell banks have been included. A qualification protocol also has been provided for manufacture of a new master cell bank. The protocols are considered acceptable and the generation and qualification of the new MCB and WCB in line with ICH Q5D.

Process validation

Several consecutive drug substance PPQ batches were manufactured at the commercial proposed site, in accordance with pre-approved protocols and according to the commercial process, scale, and control procedures. PPQ results are provided for all individual process steps and phases for process parameters as well as for process attributes/IPCs and for release testing. All process validation data are within the pre-defined ranges/acceptance criteria/specifications, including the critical parameters and attributes (CPPs, CPAs and CQAs). Impurity clearance from upstream and downstream manufacturing steps was validated, demonstrating process-related impurities clearance as well as appropriate control of product-related impurities throughout the purification process; overall, based on the results provided, the process is able to remove impurities to acceptable low levels; however, one concern is posed in relation to clearance of HCP and host cell DNA during one of the purification steps.

Refiltration of bulk drug substance due to post-use filter integrity test failure will be conducted in accordance with pre-approved protocols. Cleaning of equipment used for each of the process steps was validated; however, cleaning validation for some of the equipment is incomplete due to deviations occurring during execution of the validation protocol. Additional cleaning validation studies are programmed and results will be submitted when available; the applicant is reminded to fulfil its commitment.

Shipment of VB4-845 drug substance from the manufacturing site in United States to the finished product manufacturing site in Germany was validated.

Overall, the process validation results demonstrate that the process performed consistently and removal of impurities is generally considered adequately demonstrated, with a few points that still need to be addressed.

Manufacturing process development

During the clinical development of VB4-845, different processes were used for manufacturing of nonclinical and clinical drug substance material. The VB4-845 drug substance manufacturing process has been optimised throughout development by increasing purity, yield, and production scale. For commercial manufacturing, the process has been transferred to the proposed drug substance manufacturing site.

Process 7 is the proposed commercial manufacturing process; Process 6 material was used for Phase 3 clinical trial; Process 5 material was used for Phase 2 clinical trial; Process 2 and 3 material was used for Phase 1 clinical trial. Each process has been demonstrated to produce material that is considered to have comparable quality attributes. The changes introduced between process 6 and process 7 are considered major changes requiring a comprehensive comparability between the Process 6 clinical Phase 3 material and the Process 7 commercial material. There were no changes in protein concentration before formulation, or in formulation, between Process 6 and 7.

The drug substance process characterisation is considered acceptable and the process characterisation is considered comprehensive and adequate and complying with the general principles outlined in ICH Q11 and ICH Q6B. The definition of CQA, CPP, KPP, CPA, KPA and proven acceptable ranges is sound and the proposed control strategy for the manufacture of VB4-845 is considered supported. A few points should be addressed concerning acceptable ranges for some output parameters.

Comparability was evaluated following each process change for Process 1 through Process 7. The comparability studies have been conducted in accordance with ICH Q5E guideline *Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process*.

Overall, it is considered demonstrated, that product manufactured by the commercial process is representative of the pivotal clinical material. However, some minor concerns still need to be addressed by the applicant.

Specification and method evolution

The methods and acceptance criteria for the attributes tested using the drug substance non-compendial methods and the majority of the compendial methods are the same as the methods and acceptance criteria for drug product. Therefore, the specification and method evolution are applicable to both drug substance and drug product.

Analytical testing was performed at the development site through Process 1 to 6, where Process 7 material initially was tested as well. The methods were transferred to the proposed commercial manufacturing sites for drug substance and drug product. After the transfer, the analytical testing of Process 7 drug substance and drug product was performed at the proposed commercial sites.

During the development, the methods SE-HPLC, non-compendial protein concentration, polysorbate 80 and potency have been modified based on the equipment available at the testing site or optimised to provide better analytical resolution. One identity test method was removed as ID test of the drug substance for Process 7; the remaining three methods combined are considered sufficient to confirm molecular structure/structural integrity. New analytical methods, not previously part of the Process 6 testing, were implemented at the proposed commercial sites. Tests for purity, charge variants and osmolality were introduced.

Initial method bridging

As a consequence of the method transfer, method optimisation and introduction of new analytical test methods, method bridging studies were performed. The conclusions made by the applicant for the initial method transfer are overall not endorsed, and OC's for the individual methods have been raised.

On-going method bridging study

In addition to the bridging study performed during the initial method transfer, a bridging study is currently on-going to evaluate method comparability between the test methods run for the Phase 3 study and the proposed commercial test methods. The study includes a drug substance batch and a drug product batch. Statistical analysis using analysis of covariance (ANCOVA) was employed to compare the degradation rates of materials tested by both methods. Overall, the ANCOVA approach for method comparison is not fully understood or endorsed. The approach for the on-going method bridging study should be further discussed, explained and justified.

Potency

Information and data regarding the potency assay is difficult to comprehend, as the method has been improved, transferred between sites and the reported value has been changed from absolute IC_{50} value to relative potency. It is considered important for the consistent measurement of the potency and for the consistent efficacy of the drug product, that it is documented that the setup of the assay has been improved. Especially, it is found important whether a reference standard has been introduced from Process 6 (pivotal clinal trial). Based on these considerations, major issues are raised concerning the potency determination including the use of the reference standard and determination of method equivalence.

Endotoxin

During method development low endotoxin recovery (LER) studies have shown that the drug substance and drug product samples display LER. LER implies the reduced capability of Limulus Amebocyte Lysate based assays to detect a known amount of endotoxin spiked into a sample. To overcome LER, the applicant has evaluated that demasking of endotoxin is possible and intends to incorporate the demasking into the current endotoxin test method for drug substance and drug product. Based on LER demonstrated for the drug substance samples, the endotoxin results generated cannot be relied upon for release of the DS and DP. The applicant has been requested to generate and provide a description of a risk-based approach as an interim measure until a validated endotoxin demasking method becomes available.

Characterisation

Oportuzumab monatox drug substance has in general been appropriately characterised, however the extended characterisation of charged variants is not found sufficient.

The characterisation studies included release testing using the proposed commercial release analytical methods and extended characterisation to assess the primary, secondary, and higher order structure, as well as post-translational modifications of a Process 7 batch.

The *in vitro* biological activity of oportuzumab monatox drug substance has been determined using appropriate test methods which are also part of the release testing of the drug substance.

<u>Product related impurities/substances</u>

Potential impact of charge and size variants on potency and binding has been investigated. The impact of the charged variants on potency and binding, *i.e.* whether the various variants have similar behaviour with regard to the mechanism of action, safety and efficacy compared to the predominant form, remains to be further investigated and clarified.

<u>Process-related impurities</u>

The process-related impurities include host cell protein (HCP) and residual host cell DNA. Overall the process related impurities HCP and host cell DNA are reduced to acceptable levels. Minor issue related to the information on clearance of HCP and host cell DNA during one of the purification steps. Sufficient clearance during manufacturing has been shown for residual raw materials and processing aids. The levels of these impurities present in the drug substance is evaluated to be of no toxicological concern.

Contaminants

Endotoxins and adventitiously introduced microbial species, are evaluated through determination of endotoxin and bioburden levels during drug substance release testing for each batch. Bioburden and endotoxin are controlled by IPC testing during the manufacturing process and the downstream manufacturing process has been evaluated to reduce endotoxin. However, since DS and DP samples are affected by low endotoxin recovery (LER), a description of a risk-based approach to support the safety of the drug product with respect to endotoxin content is required.

Elemental impurities, extractables and leachables

In the case of elemental impurities, a risk assessment was conducted according to ICH Q3D. The result indicated that additional studies should be performed for some elemental impurities. The maximum allowable limit of each elemental impurity was calculated using the maximum administered daily dose and the Permitted Daily Exposure (PDE) levels indicated in ICH Q3D. Comparing to the maximum amount measured in VB4-845, a safety factor was determined for each impurity. The control threshold, defined per ICH Q3D as a level that is 30% of the established PDE, indicated a risk factor for each impurity. Based on these results, the potential process-related impurities were considered sufficiently cleared by the manufacturing process.

The applicant has used as PDE values those of oral administration, however calculations should be repeated considering the parenteral administration as the worst-case scenario for a vesical administration.

The presented risk assessment also includes an evaluation of the risk of extractables and leachables from materials used during the manufacture covering both the drug substance manufacturing process and the drug product manufacturing process. Minor issue has been identified for the single-use, polymer manufacturing equipment with respect to the risk assessment.

Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications

The proposed drug substance release specification for oportuzumab monatox includes general tests (appearance (color and clarity), pH, osmolality), test for identity, purity and impurity tests for product-related impurities, test for process-related impurities (host cell DNA, HCP), test for protein content, potency, as well as tests for safety (endotoxin and bioburden). Identical acceptance criteria for the analytical tests are applied at release and at shelf-life. Test for identity, residual HCP, residual host cell DNA, endotoxin and bioburden testing are not a part of stability testing. Overall, the parameters included in the drug substance specification are found adequate to control the quality of the oportuzumab monatox drug substance.

The justification of the acceptance criteria for oportuzumab monatox is based on batch data from drug substance and drug product batches representing manufacturing Process 6 (Phase 3 clinical studies) and Process 7 (commercial process) also including stability batch data. The applicant has been

requested to, based on the clinical experience and process capability, tighten the acceptance criteria significantly for several quality attributes for the drug substance to be in line with the requested tightening of the acceptance criteria for the drug product.

Specification acceptance criteria for safety-related attributes / process-related impurities (HCP, residual DNA, endotoxin, bioburden) were provided in the dossier. The proposed acceptance criteria for residual DNA and Bioburden are accepted, while the applicant has been requested to tighten the proposed acceptance criteria for HCP to reflect the current process capability. During method development low endotoxin recovery (LER) studies showed both the DS and the DP samples are affected by LER. Based on this, the applicant has been requested to generate a risk-based approach and to justify how the endotoxin level is controlled at DS and DP level. As part of the risk-based approach to control endotoxin levels in the DS and DP, tightening of the endotoxin acceptance criteria for the DS specification and the acceptance criteria for the DP specification has been requested.

Analytical procedures and reference standards

The applicant has provided validation reports for the non-compendial analytical methods. The non-compendial methods have in general been appropriately validated according to ICH Q2 to control oportuzumab monatox drug substance. However, several concerns have been raised regarding the validation data.

The suitability of the test for bioburden and test for endotoxin performed according to Ph. Eur. have been demonstrated for both DS, DP and IPC samples. However, since it has been shown that both the DS and the DP samples are affected by low endotoxin recovery (LER), a demasking procedure to mitigate LER will be further assessed and incorporated into the current endotoxin test method for drug substance and drug product. Confirmation that the suitability of the endotoxin test will be re-evaluated when the demasking procedure is in place has been requested, and a time-frame for the introduction of the demasking procedure and following verification of the endotoxin method is pending.

Reference Standards

Primary reference standard (Process 7) is established and has been qualified for commercial use. Qualification includes drug substance release methods as well as additional characterisation. A minor issue related to the reference standard specifications for requalification has been identified. An overview of the history of the reference standards has been provided. Information on the batch (No., date, scale) and the use of the previous reference standard are included as well as a short description of the preparation. Overall, a link between the clinical, preliminary, and the commercial reference material has been established for the proposed primary reference standard (Process 7). The assignment of potency is, however, not found adequate. Assignment of potency to the reference standard is questioned and a major objection was raised during the assessment. Therefore, a description and justification of a revised procedure for assignment of potency to the primary standard, based on statically relevant sample size and statistical analysis of the data has been requested. In addition, there are some discrepancies in characterisation results for post-translational modifications obtained during qualification of the preliminary reference material that require clarification.

Batch analysis

During the clinical development of VB4-845, seven different processes were used for manufacturing of nonclinical and clinical drug substance material: Process 7 (commercial process); Process 6 (material for Phase 3 clinical trial); Process 5 (Phase 2 clinical trial); and Process 1 - 3 material (for Phase 1 clinical trial).

Batch analyses data have been provided for all drug substance batches produced by processes 3.1 through 7. All batch data, for all processes 3.1 through 7, comply with the specifications valid at the time of testing. Data for drug substance manufactured by Process 1 to 3 are not included since the drug substance and drug product manufacturing processes at that time were consecutive with no hold step between formulation and filling; for these batches finished product batch data are provided.

Batch data have been provided for four full-scale batches produced according to the proposed manufacturing process (Process 7). The provided batch data demonstrates adequate batch-to-batch consistency. Revision of some incorrect table numbers is requested.

Container closure system

VB4-845 drug substance is stored in a 10L Low Density Polyethylene (LDPE) bag placed inside a Bioshell for storage and shipment. The product contact bag consists of an ultra-low-density polyethylene (ULDPE) product contact layer (inner layer), an ethyl vinyl alcohol (EVOH) barrier layer, and polyester elastomer (PE) outer layer. The materials of construction are compliant with European Pharmacopoeia Chapter 3.1.5 *"Materials based on polyethylene for containers and closures for preparations and for parenteral and ophthalmic use"*. The materials are also in compliance with EMA/410/01: *Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products*. The bags are sterilised by irradiation and demonstrated to be compliant with *ISO 10993; Biological evaluation of medical devices*.

Risk of leachables and extractables from the DS container closure system has been evaluated and risk-based assessment of the drug substance storage bag was performed based on the current BioPhorum Operations Group (BPOG) guidelines for extractables testing of materials that come into contact with the drug substance. The VB4-845 storage bag Leachable Risk Rating (LRR) was scored as medium risk based on a combination of storage temperature, duration, and content of PS80 (non-ionic surfactant).

Based on the medium risk, and in accordance with the BPOG recommendations, vendor-provided extractables data was used for a toxicological assessment to determine if a product-specific leachable study was warranted. The evaluation demonstrated that the extractables are more than 3- to 100-fold below the Safety Concern Threshold/Qualification Threshold (SCT/QT). Based on these results, no leachables study was required for the drug substance storage bag. However, a freeze-thaw study was conducted for volatile, semi-volatile and non-volatile organic compounds and results were evaluated against the analytical evaluation threshold (AET) which is calculated based on the threshold of toxicological concern (ICH M7) for a given impurity. The results demonstrate that there were no volatile, semi-volatile, or non-volatile organic compounds present above the analytical evaluation threshold (AET) following 3 freeze-thaw cycles of the drug substance in the intended container closure system. Further, no elemental impurities were observed above the limit of quantitation of 5 ppb.

Based on the risk evaluation and studies described above, the applicant concludes that the container closure system is considered safe for use. This conclusion is endorsed.

Stability

Drug substance stability studies are being conducted under long-term storage conditions (-20°C ± 5°C) on five process 7 (commercial process) VB4-485 DS batches and three process 6 batches. In addition, studies are being conducted under accelerated (5°C ±3°C), and stressed (25±2°C) conditions. Samples are stored in containers constructed of the same material of composition (low density polyethylene (LDPE)) as the commercial drug substance container closure system. The containers are smaller (1/20 of the volume used at manufacturing scale), but are filled at 80% fill

volume which results in a fill ratio equivalent to that used to fill drug substance containers at manufacturing scale.

The analytical methods applied include testing for appearance, pH, protein concentration, purity/impurity, potency and EpCAM binding. The stability protocols are acceptable and the studies are designed according to ICH Q5C and Q1A(R2). Overall, the selected analytical methods are considered appropriate as stability indicating methods, as demonstrated by the trends/OOS observed during storage under stressed conditions. However, major issues are identified in relation to the method used for determination of potency, also affecting the evaluation of the potency stability data. Furthermore, discontinuation of testing for bioburden going from stability studies of process 6 to process 7 batches and the use of three different specifications instead of one common set must be justified.

Stability under long-term storage conditions

The applicant has provided 12 months of real-time, real-temperature primary stability data from one process 7 DS batch. Up to 6 months of real-time, real-temperature long-term stability data have been provided for the remaining four process 7 batches (primary stability data) and also for the three process 6 DS batches (supportive stability data). The results obtained from storage under long-term conditions are all compliant with the acceptance criteria in place at the time of testing and indicate no degradational trends.

Stability under accelerated and stressed conditions

Storage under accelerated conditions (5°C±3°C) resulted in OOS for one attribute while the remaining quality attributes tested remained compliant with the acceptance criteria. Storage under stressed conditions (25±2°C) was also evaluated. The trends observed were consistent for the different batches.

Shelf-life assignment

A shelf-life of XX months is proposed for VB4-845 drug substance when stored under long-term storage conditions (-20°C ± 5°C). The data presented indicate a high level of stability of the DS. However, at present 12 months of real-time, real-temperature data have only been provided from one batch, which was re-filtrated due to process issues and deviations that arose during production. This may have impacted product quality attributes, for which reason these data should be considered independently from the pre-PPQ and PPQ batches. According to ICH Q5C primary data to support a requested shelf-life for either drug substance or drug product should always be based on long-term, real-time, real-condition stability studies. Usually for both DS and DP, stability data should be provided on at least three batches for which manufacture and storage are representative of the manufacturing scale of production. Additional stability data on the Process 7 batches are available and have been requested.

The applicant has provided acceptable post-approval stability protocols and commitments. However, not including testing for bioburden must be justified.

3.1.3. Finished Medicinal Product, VB4-845 concentrate

Description of the product and Pharmaceutical Development

Description of the product

VB4-845 drug product is a sterile concentrate for intravesical solution containing 5 mg/mL of VB4-845 formulated in sodium phosphate buffer pH 8.0 and polysorbate 80. All excipients are compendial.

Prior to administration, the drug product is diluted in VB4-845 diluent comprised of a phosphate buffered saline solution, pH 7.4 (VB4-845 Diluent).

The VB4-845 drug product container closure system consists of a 10 mL Type I clear glass vial, a 20 mm, grey chlorobutyl rubber stopper with FluroTec® / B2-40 coating and a 20 mm Flip-Off®, silver/royal blue aluminum plastic combination crimping caps. The vial and stopper comply with USP, EP and JP compendial requirements. VB4-845 and diluent is packed into two separate cardboard cartons, which are co-packed in an outer carton.

Pharmaceutical development

VB4-845 is a sterile concentrated solution which is intended for intravesical instilation after dilution with sterile PBS (diluents) to obtain a target concentration of 5 mg/mL. VB4-845 concentrated solution is formulated in sodium phosphate, polysorbate 80, pH 8.0 buffer. There are no overages in the VB4-845 drug product.

Formulation takes place during the drug substance manufacture and the drug substance and drug product formulations are identical. Excipients include disodium phosphate heptahydrate and sodium dihydrogen phosphate monohydrate (buffering agents), and polysorbate 80 (stabilising agent). All excipients are compendial grade (USP, Ph. Eur.). No novel excipients or excipients of human or animal origin have been identified. No preservatives or other additives for microbial control are used in the formulation.

Two different formulations were used to support the Phase 1 clinical studies. A third formulation was used to support the Phase 2 and Phase 3 clinical studies. The proposed commercial drug product formulation is identical to the formulation used in Phase 2 and Phase 3 clinical studies.

Different DP manufacturing processes have been used throughout development and in preparation for commercial manufacturing. Process changes were minor and included changes in lot size, fill volumes, container-closure size, as well as changes in equipment to accommodate larger lot sizes; the manufacturing process steps have remained the same throughout development. Site transfer occurred between Phase 3 clinical lots (process 6) and the intended commercial manufacturing process (process 7). A number of process technical transfer studies were conducted to support transfer and development of the proposed commercial process control strategy; the studies are comprehensive and considered adequate.

The Quality Target Product Profile (QTPP) of the product has been defined; definition included intended clinical use, mode of action, route of administration, dosage form, formulation and strength, container closure system, in-use and shelf-life stability, and drug product critical quality attributes (compliance to specification). The QTPP for VB4-845 DP was defined in accordance with ICH Q8 (R2) *Pharmaceutical development* and is considered appropriate. A risk assessment (FMEA) was used to identify critical process attributes and parameters and to design the process validation studies. The risk assessment and the scoring system is considered appropriate.

Sterility of the drug product is ensured by control of raw materials and excipients, 0.2 µm filtrations throughout the DS and DP processes, DS release specification, DP release specification, DP stability specification, control of container closure integrity, and aseptic processing (including media fills).

Sterilisation of vials and stoppers meets the criteria specified in EMA/CHMP/CVMP/QWP/850374/2015 *Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container* and is validated. Overall, the proposed drug product manufacturing process is considered justified. It is noted, that filter sterilisation and aseptic filling was chosen over terminal heat sterilisation to prevent thermal denaturation of the protein; this is considered acceptable. Furthermore, it is noted that stability of the drug product is limited at temperatures higher than -20°C; thus, although -20°C is inconvenient for transport and handling, the proposed drug product long-term storage condition is considered acceptable.

Comparability

The comparability study included a comparison of release test results from 3 lots from each of the processes 6 and 7 using the proposed commercial test methods, side-by-side forced degradation study, freeze/thaw induced stress, and photodegradation studies. Finally, data derived from long-term and accelerated stability studies were compared. Predefined comparability acceptance criteria were defined. Overall, the results from the comparability study indicates that Process 6 and Process 7 drug products are comparable. However, some points should be addressed, including failure to comply with predefined comparability acceptance criteria for purity parameters and incongruence between the applied release acceptance criteria and the proposed DP specification for potency and endotoxin.

Container closure system

The proposed commercial container closure system for the VB4-845 drug product consists of a 10 mL Type I clear glass vial, a 20 mm grey FluroTec® coated, chlorobutyl rubber stopper and a 20 mm Flip-Off® silver/royal blue aluminium plastic combination crimping cap. Information is provided in support of the chosen container closure system. The vial and stopper comply with EP compendial requirements. Extractable and leachable studies with the primary container closure system (vial and stopper) have been performed, including studies of volatile, semi-volatile, non-volatile extractables, and inorganic elements. Stability testing of the drug product supports the suitability of the proposed container closure system. The suitability of the proposed container closure system is considered adequately supported.

Compatibility

The compatibility of the drug product was addressed. Compatibility studies included dose accuracy, compatibility with alternative devices used for preparation and administration, in-use stability studies, and simulated in-vivo stability of instilled drug product. Compatibility is considered demonstrated, and the instructions for use and handling in the SPC is considered supported. However, the proposed in-use shelf life after dilution needs further support.

Manufacture of the product and process controls

Manufacture

The manufacturing process is standard and consists of drug substance thawing, pooling and mixing, sterile filtration, filling, stoppering, and capping. The final drug product is stored and shipped at -20 ± 5°C. No reprocessing is performed. A batch formula has been provided for the proposed commercial batch size. The batch numbering system is explained. No prolonged holding times are proposed; maximum process times are defined for each step and in addition a total allowable process time at

room temperature from post-thawing to storage of bulk drug product is defined. Overall, the manufacturing process and the equipment used is considered adequately described. However, one point concerning information on sterile filtration should be addressed.

Process controls

The control strategy includes control of process parameters and in-process controls for each process step, material and component specifications, product release and stability specifications, and GMP quality systems. Process parameter target values and ranges and/or limits are defined for the CPPs. The manufacturing experience is limited; thus, process parameter ranges were based on knowledge from development studies, clinical manufacturing, tech transfer from clinical to the commercial manufacturing site, and the PPQ campaign. Limits for the in-process controls are defined as appropriate. It is noted, that continuous process verification is in place and as continued knowledge is gained, adjustments to the process and/or the control strategy will be made as appropriate; as the control strategy is overall considered adequate, this approach is acceptable.

Overall, the process is considered sufficiently described and the control strategy, including process parameters and in-process controls, is considered adequate to control the process and ensure formation of drug product of adequate and consistent quality.

Process validation / verification

PPQ results on several consecutive drug product PPQ batches manufactured by the proposed commercial site are provided for all individual process steps for both process parameters, in-process controls, and for release testing. All data comply with the pre-defined process validation acceptance criteria. The proposed process parameter targets and limits for the drug product manufacturing process, including hold times and time out of refrigeration, are considered justified by the process validation. However, the demonstrated process capability points towards tightening of the release acceptance criteria.

Filter validation studies have been performed as expected. Sterility assurance included validation of sterilisation of equipment, vials and stoppers, and aseptic processing (media fills and environmental monitoring). A shipping study of VB4-845 drug product has been performed; additional studies are planned to be executed following manufacturing of the initial commercial batches. For combined pack, the applicant states that a shipping validation study specific to the EU co-packaged product will be defined and performed prior to commercialisation. Due dates for the additional shipping studies are requested.

The process validation demonstrate that the process performs consistently and the proposed commercial process is considered supported.

A PACMP is provided concerning validation of scale-up of batch size.

Product specification, analytical procedures, batch analysis

Specifications

The proposed drug product release specification for the oportuzumab monatox includes general tests (appearance (color and clarity), pH, extractable volume), test for identity, purity and impurity tests for product related impurities, test for protein content, test for polysorbate 80 content, Potency and EpCAM binding, as well as tests for safety (visible particles, subvisible particulates, endotoxin and test for sterility). The same acceptance criteria for the analytical tests are applied at release and shelf-life. Tests for identity, polysorbate 80, endotoxin testing, and extractable volume are not a part of stability testing. Container closure integrity testing (dye ingress) is included in the stability testing. The

applicant has been requested to introduce a test for osmolality for the drug product according to Ph. Eur. 2.2.35.

The justification of the acceptance criteria for oportuzumab monatox is based on batch data from drug product batches manufactured representing manufacturing Process 6 (Phase 3 clinical studies) and Process 7 (commercial process), which also include stability batch data. Some minor issues related to the batches used for setting the acceptance criteria for one particular quality atribute have been identified.

The proposed acceptance criteria are identical for release and shelf-life. The applicant has been requested to take the clinical experience into account and tighten the acceptance criteria significantly for the several specification attributes for the drug product. Convincing justification of the specification acceptance criterion for potency should be presented, and unless sufficiently justified the acceptance criterion for potency should be tightened.

Characterisation of impurities

No new impurities are generated during the drug product manufacturing process and all impurities observed in the drug product were characterised for the drug substance.

The risk of elemental impurities contamination from the components used for manufacturing of the drug substance and drug product has been evaluated and is considered negligible. The applicant has been requested to provide a risk evaluation/risk assessment for the full manufacturing process and lifecycle of Oportuzumab monatox drug product including the diluent, discussing the possible formation of and contamination with N-nitrosamines.

Analytical procedures and reference standards

The method descriptions and validations for potency and identity/relative binding can be found in the drug substance sections. The non-compendial methods are identical to the methods described for the drug substance. Differences in equipment, reagents and utensils exist, but the overall principle, the main reagents used, and system suitability test are identical between the drug substance methods and drug product methods. The analytical procedures are described in sufficient details. Information on the reference standards are included where relevant. System suitability criteria, and assay and sample acceptance criteria are specified where relevant and the acceptance criteria have been confirmed during validation of the methods. The system suitability criteria are found adequate to confirm that the methods are in control during routine testing. The methods, except potency and identity/binding, have been (re)validated at the drug product testing site and validation reports are provided. The acceptance criterions for the validation parameters are identical to the acceptance criteria for the drug substance methods.

The applicant has provided validation reports for the non-compendial methods. The non-compendial analytical methods have been appropriately validated according to ICH Q2 to control oportuzumab monatox drug product.

The suitability of the test for bioburden and test for endotoxin performed according to Ph. Eur. have been demonstrated. However, as DP samples are affected by low endotoxin recovery (LER), a demasking procedure to mitigate LER will be further assessed and incorporated into the current endotoxin test method for drug substance and drug product. Confirmation that the suitability of the endotoxin test will be re-evaluated when the demasking procedure is in place has been requested, and a time-frame for the introduction of the demasking procedure and following verification of the endotoxin method is pending.

The drug product reference material used for testing drug product is the same as the reference material used for testing the drug substance, for which issues have been identified.

Batch analysis

VB4-845 drug product has been manufactured using seven different processes (Process 1 through Process 7). Batch analyses data have been provided for all batches produced by the processes 1 through 7; the batches met the acceptance criteria in place at the time of release.

For the commercial process 7 a total of four lots of VB4-845 drug product have been manufactured at the commercial manufacturing site using the proposed commercial process; for process 6 lots, which were used in Phase 3 clinical trials and for stability, a total of sixteen VB4-845 drug product lots have been manufactured. The provided batch data demonstrate adequate batch-to-batch consistency.

It is noted, that specifications stated in Batch Analysis Results for VB4-845 Drug Product (Process 7), Tables 6 and 7, do not comply with the proposed specification for some parameters.

Container closure system

The primary container closure system for VB4-485 DP consists of a clear, 10 mL Type I glass vial, closed with a 20 mm FluroTec-coated chlorobutyl rubber stopper and a 20 mm aluminium seal. The material in contact with the DP (glass vial and rubber stopper) is of compendial quality and appropriate for storage of the VB4-845 DP. The aluminium seal (cap) is released based on vendor specifications. Upon receipt of each container closure component, the CoA is reviewed against specifications. The VB4-845 drug product vials are packed in a carton (1 vial/carton) designed to protect the vial from light and potential physical damage during handling, shipping, and storage.

For supply to users, each carton containing a single vial of VB4-845 drug product is co-packaged with a 48 mL vial of diluent in a combined outer carton, which is considered as the outer pack and complies with EU labelling requirements. The lot number applied to the co-packaged drug product (containing VB4-845 concentrate and solvent) is that of the concentrate.

The information provided on the container closure system selected for storage of VB4-845 is adequate and the system is considered fit for the purpose. However, practical issues are foreseen for the co-packaged VB4-845 DP and diluent, as these must be stored at different temperatures.

Stability of the product

Stability studies are being conducted under long-term (-20°C ± 5°C) and accelerated storage conditions (5°C ± 3°C) for DP manufactured using DS from process 3, 3.1, 5, 4 (preliminary studies), 6 (supportive study) and 7 (primary study, commercial process), and in addition under stressed storage conditions (25°C ± 2°C) for process 7 derived DP.

The stability protocols are acceptable and the studies are designed according to ICH Q5C and Q1A(R2). Quality attributes (potency, purity, content), general attributes (pH, appearance), and sterility have been addressed from process 3.1 derived DP and onwards. Overall, the selected methods are considered appropriate as stability indicating methods, however, major issues are identified in relation to the cell-based assay applied for potency testing, which also affects the stability studies**.**

The container closure system and filling volume used during stability studies is considered representative.

Long-term storage conditions

At present, 6 months of real-time, real-temperature primary stability data (DS process 7) have been provided from one PPQ batch manufactured at the commercial drug product manufacturing site. In addition, 12 months of real-time, real-temperature data have been provided for one pre-PPQ batch manufactured from the first process 7 DS batch; these data are, however, only considered supportive, as the DS batch was affected by issues during manufacture. Furthermore, supportive real-time, real-temperature data ranging from 36 to 74 months have been provided for six DP batches manufactured from process 6 DS material. Of these, at least 48 months of data are provided for five DP batches.

From process 3.1 DS and onwards, all stability results obtained from storage at the current long-term storage temperature of -20°C ± 5°C have been compliant with the acceptance criteria in place at the time of testing. A slight tendency of decrease in monomeric purity was observed for DP manufactured from process 3.1 and 4 DS, however, from process 5 and onwards, this trend was no longer observed. For the process 6 and process 7 derived DP, a slight decrease in potency is observed as shown by regression analysis, but results remain within specification up to 74 months.

Accelerated and stressed storage conditions

Up to six months of data have been provided from studies under accelerated conditions (5°C ± 3°C) of the drug product PPQ lots manufactured using the proposed commercial manufacturing process (Process 7) and the new commercial drug product manufacturer. Three weeks data have been provided from one PPQ batch stored under stressed conditions (25°C ± 2°C). During storage under accelerated conditions, all data were within the specification, while OOS data were obtained during storage under stressed conditions. The data obtained, indicate that the drug product is stable for 2 months when stored at 5 ± 3°C and that the product degrades within days, when stored at 25°C ± 2°C.

Photostability studies

Photostability studies were conducted in line with ICH Q1B. The results demonstrated that VB4-845 is photolabile when exposed to extreme light intensity and should be protected from light and the secondary packaging provides this protection.

Shelf-life

A shelf-life of 48 months has been assigned to the process 7 DS (commercial) derived VB4-845 when stored at -20°C ± 5°C. As comparability has been demonstrated between DS process 6 and process 7 derived DP, the assigned shelf-life is considered supported by the data provided and thus overall acceptable. However, final conclusion on shelf-life awaits resolving of the major objection raised in relation to the cell-based potency assay. It is noted that the storage conditions proposed for the concentrate (-20°C) are inconvenient for transport and handling. However, the stability data obtained during storage at accelerated or stressed conditions do indeed justify the storage conditions proposed, as degradation is observed when the VB4-845 DP is stored at 5° C ± 3°C.

For supply to users, each carton containing a single vial of VB4-845 drug product is co-packaged with a 48 mL vial of diluent in a combined outer carton. Practical issues are foreseen with regards to storage, transport, and generally handling of the proposed co-packaging, as the VB4-845 DP must be stored at -20°C while the VB4-845 diluent must be stored at 25°C. The handling of these must be clarified.

Biosimilarity

Not applicable.

3.1.4. Finished Medicinal Product, Diluent

Description of the product and Pharmaceutical Development

Description of the product

The VB4-845 diluent is a sterile, colourless aqueous solution used for diluting VB4-845 drug product prior to intravesical instillation. VB4-845 diluent is formulated with monobasic potassium phosphate, dibasic sodium phosphate and sodium chloride at pH 7.4. All components are compendial.

Each vial contains a nominal fill volume of 48 mL. There are no overages in the production of VB4-845 diluent. There is no overfill in the vial. The appropriate dose of VB4-845 drug product (33 mg) can be withdrawn and administered following dilution of VB4-845 drug product concentrate in the PBS diluent.

The combined pharmaceutical dosage form is defined as a concentrate and solvent for intravesical solution.

The VB4-845 diluent container closure system consists of a 100 mL Type I clear borosilicate glass vial stoppered with a 20 mm, grey chlorobutyl rubber stopper with FluroTec® / B2-40 coating and sealed with a 20 mm combination aluminium plastic crimping cap. The vial and stopper comply with compendial requirements.

VB4-845 drug product and diluent are packed into two separate cardboard cartons, which are co-packed in an outer carton.

The VB4-845 diluent is an isotonic, phosphate buffered saline (PBS) solution (pH 7.4) for dilution of the VB4-845 DP. The formula of the diluent has been developed to match commercially available PBS. The diluent neither contains any novel excipients nor any components of human or animal origin.

Development of the Manufacturing Process

For commercial purposes, the proposed manufacturing process includes compounding, sterilising filtration through two 0.22 µm filters, and aseptic filling at the proposed commercial diluent manufacturing site.

The proposed commercial process was selected based on platform knowledge, process development studies as well as studies conducted during the technical transfer between the development and the commercial sites.

Elemental impurity assessment has been conducted, demonstrating that no elemental impurities of toxicological concern are present in the VB4-845 diluent samples.

Quality target product profile (QTPP) and critical quality attributes (CQAs) have been defined according to ICHQ8 (R2). The QTPP and CQAs defined are considered appropriate.

Product parameters (PP) were ranked pre-PPQ based on a risk assessment, accounting for factors that control product quality and process performance, and re-evaluated after PPQ. The CPPs are considered appropriately identified, and are found to be adequately controlled by the in-process controls conducted.

The specifications for the diluent comply with compendial requirements. Upon transfer of the manufacturing process to the proposed commercial site, several changes to the quality attributes and/or methods used have been introduced. All lots manufactured at the development and commercial sites meet release specifications and show comparable quality attributes.

The VB4-845 diluent solution has been demonstrated to be compatible with VB4-845 drug product. The diluent composition and diluent container closure format has remained the same throughout clinical development and is the same as that proposed for commercialisation.

Manufacture of the product and process controls

VB4-845 diluent is manufactured at a site in USA. GMP certificates are provided for all manufacturing/testing sites, except for one testing site in USA. The applicant is requested to provide a valid GMP certificate for this testing site.

The manufacturing process consists of compounding, sterile filtration, aseptic filling, stoppering, capping, inspection, and storage.

Five critical process parameters (CPP) have been identified. The CPPs identified are considered adequately controlled by the in-process controls (IPCs) in place. The acceptance criteria defined for the IPCs are considered appropriate. The direct product contact equipment is single-use and sterilised by gamma-irradiation or autoclaving, using validated procedures.

The process validation studies were provided in the dossier. All validation criteria and all IPC and release acceptance criteria were met. The confirmation of the adequacy and suitability of the VB4-845 diluent manufacturing process performed, was demonstrated by the manufacturing of three consecutive successful Process Performance Qualification (PPQ) lots. The PPQ lots were produced under normal manufacturing conditions according to the master batch record and as described in the process validation protocol.

The manufacturing process for VB4-845 diluent is considered appropriately validated and controlled, ensuring consistent manufacture of diluent of the intended quality.

Shipping validation has been performed for intra-USA transport. To date, one of three shipments planned have been successfully completed. The applicant states that the two remaining studies for intra-USA shipment and shipping validation studies for transport from US to EU will be conducted prior to commercialisation. Due dates for the additional shipping studies are requested.

Product specification, analytical procedures, batch analysis

Specification

The diluent is tested for quantity, quality and safety using compendial methods, including testing for appearance, visible particles, osmolality, pH, subvisible particles, endotoxin (release testing only), and sterility. Container closure integrity is tested during stability studies.

Analytical procedures and validation

The compendial procedures for appearance, pH, osmolality, and subvisible particulate matter were verified to be suitable for use. Method verification was conducted in accordance with principles outlined in European Pharmacopoeia General Notices. In addition, the endotoxin and sterility test methods were qualified for use with VB4-845 diluent demonstrating recovery of challenge organisms in the presence of product. Overall, the methods selected are considered appropriate. However, the analytical methods applied for appearance, osmolality and container closure integrity should be performed according to Ph. Eur. (and not USP) unless otherwise justified.

Batch analyses

A total of three lots, the three PPQ batches, have been manufactured at the proposed commercial site and scale. A total of 39 VB4-845 diluent lots have been manufactured at the development site for use in Phase 3 clinical trials. The specifications have remained the same throughout clinical studies and each of the diluents used in the clinical studies have met the specifications. The batch release data demonstrate consistent quality of the diluent throughout development and PPQ (commercial purposes).

Characterisation of impurities

The potential impurities in the VB4-845 diluent are derived from the excipients. No additional impurities form during the diluent manufacturing process. A risk evaluation for possible contamination with nitrosamines of the VB4-845 concentrate or diluent has not yet been conducted.

Justification of specification

The current acceptance criteria are based on compendial requirements, product formulation, and product knowledge derived from release and stability testing from the three PPQ batches and clinical phase 3 batches. The phase 3 batch data are considered representative of the data for all clinical trial VB4-845 diluent lots as no changes have been introduced to the manufacturing process throughout the clinical studies. The limits should, however, be re-evaluated upon manufacture of a sufficient number of batches.

Reference standards or materials

No reference standards or materials are used to test and release VB4-485 diluent. This is acceptable as none of the analytical methods applied requires the use of a reference standard.

Container closure system

The primary container closure system for VB4-485 DP consists of a clear, 100 mL Type I glass vial, closed with a 20 mm FluroTec-coated chlorobutyl rubber stopper and a 20 mm aluminium seal. The diluent container closure system is essentially the same container closure system as the one used for VB4-845 DP, except for the difference in vial size. Drawings and description of critical dimensions have been provided. The material in contact with the DP (glass vial and rubber stopper) is of compendial quality and appropriate for storage of the VB4-845 diluent. The aluminium seal (cap) is released for use based on vendor specifications. Upon receipt of each container closure component, the CoA is reviewed against specifications. The VB4-845 diluent vials are packed in a carton (1 vial/carton) designed to protect the vial from potential physical damage during handling, shipping, and storage.

A risk assessment for elemental impurities has been performed concluding that they are not observed above the control threshold levels. Monitoring of elemental impurities leaching from the CCS during storage will be conducted during stability studies.

For supply to users, each carton containing a single vial of VB4-845 drug product is co-packaged with a 48 mL vial of diluent in a combined outer carton, which is considered as the outer pack and complies with EU labelling requirements. It is stated that the final shipping configuration will undergo validation prior to commercialisation. Due dates for the additional shipping studies are requested.

The lot number applied to the co-packaged drug product (containing VB4-845 concentrate and solvent) is that of the VB4-845 concentrate.

Overall, the information provided on the container closure system selected for storage of VB4-845 is adequate and the system is considered fit for the purpose.

Stability of the product

Stability studies are conducted on three commercial VB4-845 diluent lots (the three PPQ batches), which have been placed upright and inverted for 48 months under long-term storage conditions (25°C ± 2°C / 60% ± 5% RH) or for 6 months under accelerated storage conditions (40°C ± 2°C / 75% ± 5% RH). In addition, ancillary stability studies are performed on inverted vials, stored for 6 months at -20°C. Six phase 3 clinical diluent batches have been placed on stability at upright or inverted positions at ambient temperature of 15-30°C.

The protocols are in accordance with current guidelines. The stability specifications applied for commercial VB4-845 diluent lots are identical to the ones used for release testing, with minor exceptions. The filling volume and container closure system used during stability studies are identical to the one proposed for commercial purposes.

For supply to users, each carton containing a single vial of VB4-845 drug product is co-packaged with a 48 mL vial of diluent in a combined outer carton. Practical issues are foreseen with regards to storage, transport, and generally handling of the proposed co-packaging, as the VB4-845 DP must be stored at -20°C while the VB4-845 diluent must be stored at 25°C. The handling of these must be clarified.

Stability data are provided for up to 48 months under long-term storage conditions for two batches of phase 3 clinical material, while data for up to 36 months are provided for five phase 3 clinical batches. Due to a deviation, sterility testing was not performed at T=36 and T=48 months for one batch. Compliant data from endotoxin testing has, however, been provided. All data from the phase 3 clinical batches are compliant with the specifications in place at the time of testing.

At present, no long-term stability data are provided from the commercial diluent lots, while T=1 month data have been provided from the accelerated and ancillary studies. The data provided are compliant with the stability specifications for commercial diluent.

Shelf-life

A shelf-life of 36 months has been assigned to the VB4-845 diluent, when stored at 25°C ± 2°C. However, no real-time, real-temperature stability data have been provided from studies performed under long-term storage conditions with commercial diluent lots. Further justification and currently available stability data must be provided before a final conclusion can be drawn with regards to the proposed shelf-life.

The applicant commits to accomplish a leachable study with one of the PPQ lots at the accelerated temperature condition for 12 months to monitor for elemental impurities leaching from the container during storage.

Biosimilarity

Not Applicable.

Post approval change management protocol(s)

Three post-approval validation protocols have been provided in relation to reprocessing and scale-up. During the assessment, several concerns have been raised in relation to the PACMPs.

Adventitious agents

Non-viral agents

No animal or human derived raw materials are used for the manufacture of VB4-845. For generation of cell banks, tryptone derived from bovine milk or of porcine origin, has been used. The tryptone used was compliant with the EMA *Note for Guidance on Minimising the Risk of Transmitting Animal*

Spongiform Encephalopathy Agents via human and Veterinary Medicinal Products, Revision 3 (EMA/410/01 rev. 3). The cell banks have been tested according to ICH Q5D, confirming microbial purity and absence of bacteriophages.

Testing is performed at appropriate stages during manufacture (IPC and/or release of DS and DP) for bioburden and endotoxin levels and for sterility. However, after the addition of the formulation buffer the DS samples are affected by Low Endotoxin Recovery (LER) and the applicant has been requested to provide a description of a risk-based approach for endotoxin control for release of DS and DP. The manufacture of VB4-845 is performed under aseptic conditions in a controlled environment according to cGMP. The risk of transmitting adventitious non-viral agents is considered negligible.

Viral agents and mycoplasma

As VB4-845 is manufactured in a prokaryotic *E. coli* cell line, the risk of propagating and transmitting adventitious viruses or mycoplasma to human beings from the product is negligible.

Conclusion

Overall, VB4-845 is considered safe for use with regards to lack of risk for transmission of adventitious agents. However, clarification on the endotoxin control is pending before a final conclusion can be drawn.

GMO

Not Applicable.

3.1.5. Discussion and conclusions on chemical, pharmaceutical and biological aspects

The quality part of the dossier presented in support of the Marketing Authorisation Application for Oportuzumab monatox drug product is of adequate quality. After the assessment of the information available, it is concluded that, from a quality point of view, Oportuzumab monatox drug product could be approved provided that the applicant resolves the List of Questions. Information and data regarding the potency determination is difficult to comprehend and is scattered across different sections in the dossier involving both drug substance and drug product sections. Since potency determination is essential for the safety and efficacy for the drug product, a major objection has been raised encompassing the issues identified throughout the dossier. Furthermore, a major objection has been raised due to the lack of a risk evaluation for the potential formation of and contamination with N-nitrosamines in VB4-845 DP and diluent, respectively.

Overall the proposed drug product manufacturing process is considered justified and the control strategy is considered sufficient to assure consistent and adequate quality of the product. Furthermore, the batches used in clinical trials are considered comparable to the commercial product. However, a number of other concerns are posed; these include *e.g.* request for tightening the specifications for drug substance and drug product which are considered too wide, request to introduce a release test for osmolality for DP, justification of the endotoxin level at final DS and DP at release as well as re-evaluation and verification of the endotoxin test, and characterisation of the charge heterogeneity of drug substance.

Three different PACMP have been submitted with the application. A few other concerns have been raised which needs to be addressed prior to the approval of the PACMPs.

A shelf-life of 48 months for VB4-845 DP is considered supported. However, final conclusion on shelf-life of the DP awaits resolving of the major objection raised in relation to the potency assay. In

addition, final conclusion of the proposed shelf-life for VB4-845 diluent (24 months) awaits updated primary stability data.

3.2. Non-clinical aspects

3.2.1. Pharmacology

Mechanism of action

VB4-845 is a recombinant fusion protein consisting of a tumour-targeting, humanised, anti-epithelial cell adhesion molecule (EpCAM) single-chain antibody fragment genetically linked to the truncated form of Pseudomonas exotoxin A (ETA252-608) that lacks the cell binding domain.

VB4-845 is believed to act through a dual mechanism of action. The first involves toxin-mediated killing following the specific binding and internalisation of VB4-845 to EpCAM overexpressed on the tumour cell surface resulting in inhibition of protein synthesis and ultimately apoptotic cell death. The second mechanism is believed to involve the development of an adaptive T cell-mediated anti-cancer response subsequent to the appearance of immunogenic cell death (ICD) markers elicited during VB4-845 tumour cell killing.

The binding affinity of 4D5MOCB to EpCAM was conserved relative to the original humanised fragment 4D5MOCA. The binding affinity of radio-labelled VB4-845 was also confirmed using SW2 cells in an RIA assay, and the KD was determined to be 4 nM [Di Paolo et al., 2003].

The binding of VB4-845 to epithelial tumour cell lines was assessed by flow cytometry using a panel of human tumour cell lines derived from various epithelial cancers, including bladder cell lines (VBRR0265). VB4-845 exhibited binding to the majority of tumour cell lines tested and was most reactive against gastric, bladder, ovarian, esophageal, prostate and cervical tumour cell lines but was not reactive against melanoma cell lines.

Immunohistochemical analysis was conducted to assess the binding of VB4-845 in Bladder and Head & Neck cancers of different phenotypes and prognoses. Tissue staining with VB4-845 was preferentially membranous. The bladder tissue micro-arrays (TMA) included various disease stages and grades. The frequency of VB4-845 binding was 62%. Association between VB4-845 staining and invasive, high grade cancers was observed. No association was found with histological subtypes. However, adenocarcinomas, adeno-squamous, and small cell carcinomas showed a high level of VB4-845 staining but due to small sample size were not statistically significant (VBRR0294).

In line with the ETA mechanism of toxicity, VB4-845 inhibited protein synthesis in EpCAM-positive SW2 (small cell lung carcinoma) cells in a dose-dependent manner with an IC50 of 0.01 pM. No IC50 could be determined with the EpCAM-negative control cell line RL (non-Hodgkin's lymphoma). Results also demonstrated that VB4-845 is specific in its targeting ability as EpCAM is required on the cell surface to mediate pharmacological activity (Di Paolo et al., 2003).

VB4-845 is believed to act through immunogenic cell death (ICD) as well. This was confirmed in a study using a tumour cell line SW-480 (VBRR0831) in which it was shown that VB4-845 cytotoxicity induces ICD biomarkers that promote an anti-tumour T cell mediated response. These biomarkers were calreticulin, ATP and HMGB1 protein, so-called "eat-me" signals.

Potency and selectivity

VB4-845 appears to very potently bind and kill certain EpCAM positive tumour cell lines, especially of bladder origin (VBRR0359). However, in this study, a normal kidney cell line was also targeted,

meaning in this instance/organ no selectivity could be shown. In light of the moderate binding of VB4-845 to kidney tissues (VBRR0285) and risk of retrograde flow during treatment, the clinical relevance of this finding should be discussed.

In study VBRR0265, 14 bladder cancer cell lines were tested and 11 of these were sensitive to VB4-845 toxicity with a wide potency range of 0.001 to 320 pM, (8 below 1 pM), confirming bladder as a suitable target of VB4-845. For most cell lines, 94-99% of the tumour cells were killed after exposure to oportuzumab monatox for 72 hours. However, for three bladder cancer lines (T-24, HT-1197 and HT-1376), only 70-80% of cells were killed after 72 hours of incubation with oportuzumab monatox, with a sub-population containing 20-30% of tumour cells remaining viable. The applicant should discuss to what extent these results could translate to a lower efficacy of oportuzumab monatox for any particular group patients.

In study VBRR0366 the potency and functional activity of VB4-845 was compared to small molecule chemotherapeutic agents using a panel of 6 different human urothelial carcinoma cell lines. In most instances, except for cell line TCCSUP, VB4-845 was the most potent. Moreover, it was shown that that, unlike gemcitabine or mitomycin C, VB4-845 does not seem to promote an immunosuppressive environment that may dampen an anti-tumour immune response.

In conclusion, VB4-845 appear to show relevant potency and selectivity in the treatment of bladder cancers, and *in vitro* proof of concept is considered established for a dual mechanism of action. However, selectivity to normal renal cells should be further discussed, since renal toxicity was observed in clinical trials.

***In vivo* Pharmacology**

Athymic mice bearing tumour xenografts derived from the Ep-CAM-positive cell lines CAL27 (tongue), HT29 (colorectal), and SW2 (lung) and the Ep-CAM-negative cell line COLO320 (colorectal) were treated i.v. every second day with either 5 of VB4-845 for a total of nine doses (total dose 45 µg) or with 10 µg every second day for a total of three doses (total dose 30 µg). VB4-845 showed reduction in tumour size for all three EpCAM positive tumour grafts. SW2 and CAL27 showed no difference in response between the two dosing schedules, whereas for HT29, the more frequent dosing appeared to be much more efficient in reducing tumour size. Hence, for some types of cancer a more consistent exposure may be necessary for relevant response.

To avoid or minimize systemic toxicity of the ETA component of VB4-845, a study using intratumoural delivery was conducted in the same model as in the Di Paolo study (VBRR0299). Mice bearing Ep-CAM-positive SCCHN human tumour xenografts (average initial tumour size, 90-150 mm^3) were treated peritumourally with VB4-845 at doses of 5 µg every other day for 3 weeks (cumulative dose, 45 µg). Control mice bearing Ep-CAM-positive SCCHN human tumour xenografts were left untreated. Each injection was distributed into 3 injection spots. Tumour growth was monitored for 76 days in the treated group and for 50 days in the untreated group after the start of treatment. The long-term effect of VB4-845 demonstrated that this treatment regimen resulted in a persistent inhibitory effect with an approximately 53% reduction of initial tumour volume maintained for at least 76 days. Moreover, CAL-27 tumour growth was reduced by approximately 12-fold on Day 50 in comparison to the untreated control. From study VBRR0299, applicant concluded that direct peri-tumoural administration of VB4-845 effectively inhibited tumour growth of an EpCAM positive cell line (CAL27, tongue) and was well-tolerated. This may be agreed, however, the report on this study appear somewhat limited in detailing the specifics of the study and raw data on the control group is missing. More details on the animal model and raw data on the control group should be provided as well as a justification for not treating the control group with vehicle.

The potential for increasing the tumour-reducing effect by co-administration with a PD-1 inhibitor (i.p.) on other tumours than the one directly injected with V-845 was evaluated in study VBRR0790. Some difference was observed, however statistical significance (N=5) was not evaluated and the clinical relevance of the size of the effect compared with PD-1 or VB4-845 alone might be questionable. The combination with PD-1 inhibitors is not in scope for the sought indication.

Secondary Pharmacology

In order to further substantiate mechanism of action of VB4-845, Study 08/373 showed that in a breast cancer stem cell assay of formation of mammospheres, VB4-845 act cytotoxic and not cytostatic on cancer stem cells in suspension with very high potency. At 4 pM, all cells were killed.

Cross reactivity

Normal Human tissues

Immunohistochemical analyses evaluated the extent of reactivity of VB4-845 with normal human tissue [VBRR0285]. applicant selected a total of 38 tissues representative of the panel of normal tissues recommended by the FDA, including tissues known to express EpCAM (US FDA, 1997). It was concluded that the staining followed the expected distribution of EpCAM in normal tissues in which VB4-845 showed strong reactivity against breast, cervix, colon, fallopian tube, gall bladder, pancreas, parathyroid, pituitary, testis, thyroid, and uterus demonstrating that VB4-845 is not suitable for systemic administration. Moderate binding was observed in kidney, parotid, prostate, small intestines and trachea. An OC on the many strong and moderate binding tissues is raised in connection with the Risk Management Plan. VB4-845 showed low levels of binding in bladder, lung, stomach, ureter, esophagus, skin, thymus and tongue confirming VB4-845 suitability for bladder instillation. This was confirmed in study VBRR0277, where binding to normal bladder and bladder cancer specimens were compared. However, normal bladder samples, were not devoid of staining.

No binding was observed in normal non-epithelial tissues such as adrenal, bone marrow, brain, cerebellum, cerebral cortex, heart, lymph node, skeletal muscle, ovary, placenta, spinal cord, spleen, tonsil and white blood cells (WBC). Liver sections only showed positive staining that was limited to the bile duct epithelium with no staining of hepatocytes [Balzar et al., 1999]. Most staining was membrane-associated with minimal cytoplasmic staining. No nuclear staining was observed in any of the tissue specimens.

Animal tissues

VB4-845 did not exhibit any cross-reactivity against a selected panel of tissues from Rhesus monkey, Cynomolgus monkey, dog, rat, rabbit (bladder not tested), or mouse. This is in line with poor sequence homology (~80% in mouse and rat) of EpCAM between humans and animals. Hence, the findings of local inflammation and necrosis observed in the general toxicology studies are not as a result of tissue selective EpCAM binding of VB4-845, but more as a result of the toxic payload in itself, the ETA, when delivered by the s.c. route of administration.

As expected chimpanzee shows relevant cross reactivity, however this species is not considered relevant for non-clinical testing.

VB4-845 is not a substrate of MDR1, hence tumours are not expected to be able to evade treatment due to this mechanism.

Safety Pharmacology

Safety pharmacology assessment was performed as part of the 4-week toxicity study in monkeys using 1 dose/week. It is acceptable not to present stand-alone studies for monoclonal antibodies (ICH S6). No effects on CNS or cardiovascular function was observed. However, Iit should, however, be mentioned that systemic exposure was documented only for the first dose (0-24 hours), probably due to neutralising antidrug antibodies. The neurological evaluation was performed pre-dose and at the end of the study (4 weeks) and at the end of recovery (6 weeks after the first dose). Hence, the potential for VB4-845 causing any direct neurological effects during exposure has not been evaluated. ECGs were obtained also on Day 1 showing sinus tachycardia, which were not attributed to VB4-845. No specific timepoints were presented for the ECG. Considering the short half-life of VB4-845, again the level of exposure during the safety assessment is not substantiated. Respiratory function appears not to have evaluated during exposure.

The evaluation of safety pharmacology is not considered sufficient. The following deficiencies should be justified: i) Potential neurological effects of VB4-845 has not been evaluated during systemic exposure, ii) Lack of specific timing for ECG, iii) The lack of evaluation of respiratory safety. Furthermore, the results from evaluation of safety pharmacology parameters in the toxicity study, showed sinus tachycardia in two animals at the mid dose (175 µg/kg/day) at four separate intervals, three of which were post dose, and at the high dose (350 µg/kg/day) in one animal at one interval which was during the recovery period. The relevance of these findings should be further discussed.

Pharmacodynamic drug interactions

VB4-845 is not intended for co-administration for the sought indication. Nevertheless, as polypharmacy in cancer treatment is common, it seemed prudent to include an *in vitro* study (CAL27 cell line) using co-administration of VB4-845 with a range of commonly used chemotherapeutic agents (VBRR0309). For most instances additivity of effect could be observed, however it should be noted that no benefit was observed when co-administered with methotrexate. A similar study was conducted using radiotherapy as co-treatment. Co-treatment with radiotherapy resulted in either synergistic or additive effect dependent on timing of treatments. No antagonistic effects were observed (VBRR0343).

3.2.2. Pharmacokinetics

VB4-845 is indicated for twice weekly intravesical administration.

The recommended dosing regimen for VB4-845 is twice weekly for six weeks, followed by once weekly for six weeks (SmPC).

However, all PK and distribution studies are performed with either intravenous or subcutaneous administration, performed in order to support systemic or intratumoural indications intended originally for more than 10 years ago. The applicant states that systemic absorption from the urinary bladder is very limited and only very low plasma levels close to LLOQ was observed in a few patients (SmPC). Despite these statements, cases of liver toxicity and kidney failure was observed in patients indicating systemic absorption from the urinary bladder or at least absorption to kidney and thereafter liver.

It is acknowledged that the nonclinical studies at least on Day 1 provide higher systemic exposure than apparently observed in the clinical setting, however this may not support investigation of issues of kidney failure or liver toxicity as observed in the clinical studies. Moreover, lack of GLP compliance of bioanalysis and documentation of systemic exposure beyond Day 1 of the general toxicity study in monkey (toxicokinetics) due to neutralising antidrug antibodies triggers a general major objection on the nonclinical pharmacokinetic programme, since patients are exposed for up to 12 weeks, and obviously animal models did not show sufficient exposure to cover this treatment period in the clinical setting.

As a first step in the characterisation of the systemic safety profile of oportuzumab monatox after intravesical administration, the possibility for systemic absorption after intravesical instillation of VB4-845 should be investigated from the clinical point of view (see clinical safety MO). In addition, the applicant is asked for a thorough discussion of the mechanism behind and clinical relevance of renal and hepatic toxicities, as well as for the elevated platelet levels, observed in the nonclinical and clinical studies. If the risks cannot be adequately characterised by these both approaches, a new distribution study using radiolabelled VB4-845 installed into the bladder of rats should be performed. Whether the study should include both single and repeat-dose should be thoroughly justified, i.e. be in line with timing of findings in the clinical setting.

Methods of analysis

Bioanalytical methods presented to support documentation of exposure in repeat-dose toxicity studies:

RAT

Report VBRr0267 entitled Development and Validation of ELISA-Based lmmunoassays for Detection and Quantification of VB4-845 and Pseudomonas Exotoxin A from Rat or Human Plasma is issued by Viventia Biotech Inc. 23 Sept 2003. This validation report describes an acceptable inter assay precision and accuracy within a very narrow dynamic range of 2 to 10 ng/mL for both analytes. No other validation parameters such as stability or dilution integrity were tested, hence the method cannot be deemed reliable. The repeat-dose toxicity report VBRR0301 is not including a bioanalysis report, only toxicokinetics reporting on the s.c. and i.v. of the highest dose of 77.8 µg/mL. Hence, exposure at doses 1.0, 5.0 and 35 µg/kg and assay performance are not accounted for. However, since severe systemic toxicity was observed after administration of 77.8 µg/kg by the intravenous route and local reactions after the subcutaneous route, exposure can be anticipated.

An ELISA immunoassay was developed for measuring the ETA concentration in rat plasma, but pharmacokinetic analysis of ETA in non-clinical species has not been provided. The applicant is asked whether these analyses were performed and for their results if they are available in order to determine the possibility of generation free active toxin levels in the systemic circulation after administration of oportuzumab monatox and its potential clinical consequences.

MONKEY

SOP 15.1.36 is a standard operating procedure for quantifying VB4-845 in cynomolgus plasma. The document is issued by Viventia Biotech Inc. on 23 Nov 2007. No validation report for this bioanalytical method is available. Moreover, the bioanalytical study report is not providing data on assay performance, dilution or reanalysis, only study sample results. It should be noted that the dynamic range for the method is only 10 to 50 ng/mL. Hence, the reliability of toxicokinetic data for the monkey may not be considered reliable. However, a new study in monkey using s.c. administration will not be required as this will be of limited relevance for the sought indication. In the GLP toxicity study in cynomolgus monkeys, the toxicokinetic analysis was not in accordance with GLP regulation. Moreover, the qualification/validation report for detection of oportuzumab monatox in cynomolgus monkey plasma as well as of anti-drug antibodies in rat and monkey are unavailable and are not being submitted in the MAA. The applicant is asked to clarify on the aspects on the toxicokinetic analysis that were not according to GLP and the impact of methodology deficiencies (non-GLP compliance and lack of validation reports) on the toxicokinetic and immunogenicity evaluation in animal studies.

Report VBRr0527 intitled Qualification of an MTS-based assay for the detection and evaluation of neutralising antibodies in plasma of Cynomolgus Monkeys used to evaluate the toxicity of VB4-845 is issued by Viventia Biotech Inc. 17 Oct 2007. This report is describing the validation of an assay to

monitor monkey plasma for VB4-845 neutralising antibodies. Although the validation is not stated to be formally GLP compliant, the manager of Quality Assurance at Viventia Biotech Inc. has signed the report. Since, GLP compliance of validation of bioanalytical methods was not mandatory in 2007, this validation is considered adequate. The validation concluded the following:

It was demonstrated that 1) the % neutralising effect is related to the concentration of anti-ETA antibody, 2) a 1/1000 dilution of cynomolgus plasma is required to eliminate any neutralising effect from the plasma itself, 3) when used as a positive control the VB4-845 neutralising effect is specific to anti-ETA antibodies, 4) the medium and high titre samples give reproducible neutralising titres between the wells of a plate, between plates on the same day and on different days and between analysts and 5) the samples are stable after 5 freeze/thaw cycles.

Absorption

RAT

Limited data on pharmacokinetics in rats was presented. In a repeat-dose toxicity study, only the high dose of 77.8 µg/kg was subjected to pharmacokinetic investigation after s.c. and i.v. administration, hence dose-linearity was not accounted for. Moreover, the selection of sampling time points for s.c. administration is not covering the elimination phase (6-24 hours). Therefore, the bioavailability may be underestimated. Only data from Day 1 is considered of value for pharmacokinetic calculations. Exposure on Day 7 using intravenous administration was much lower compared to Day 1 for unknown reasons as stated by the applicant. It should be noted that fourteen (7 male and 7 female) high dose main Study animals, dosed by the intravenous route, died within 3 to 10 days after initiation of dosing. Likewise, five (1 male and 4 female) high dose – TK group animals, also dosed by the intravenous route, died within the same time period. In total 19 animals (8 male and 11 female) died or were sacrificed moribund as a result of i.v. administration of VB4-845 at 77.8 µg/kg. Hence, odd PK data for Day 7 could be due to animals being in poor condition, preventing proper intravenous administration. On Day 1 after subcutaneous administration, bioavailability was estimated to 13%, Tmax at 4 hours, Cmax at 50 ng/mL and half-life 2.3 hours. After intravenous administration on Day 1, clearance and Vd was estimated to 24 mL/kg/h and 80 mL/kg, respectively. No obvious gender differences were observed. The applicant should discuss the reasons leading to reduce oportuzumab monatox plasma levels in rats and the role of ADAs in rat exposure levels after repeated oportuzumab monatox administration. Moreover, In SmPC, it is stated that Oportuzumab monatox was found to be immunogenic in the rat, with anti-drug antibodies observed after 7 days of dosing. This is not correct. Antidrug antibodies were measured on Day 21, 14 days after the last of 7 once daily doses, hence SmPC should be revised accordingly. The same is observed in RMP: Antidrug antibodies are stated to be found in rats already after 7 days of dosing. This could not be confirmed in the documentation. Please elaborate or revise RMP and justify the relevance of this issue to be included in the SmPC.

MONKEY

Toxicokinetics was presented for monkey in a 4 week repeat dose toxicology study. Monkeys were dosed at levels of 35, 175, and 350 µg/kg administered s.c. weekly for 4 weeks. The plasma samples were collected from all 36 main study group animals following the first and fourth doses at 7 sampling times points (prior to dosing and 0.25, 0.5, 1, 2, 4- and 24-hours following dose administration).

Exposure increased with dose on Day 1 between the low and the mid dose, however the increase was higher than the increase in dose. This is most likely due to the lowest dose being only 25-54% of the nominal dose (35 µg/mL) as stated in the Dosing analysis report. No increase was observed between the mid and the high dose. On Day 22, no exposure was observed, most likely due to antidrug antibodies. There are discrepancies between the data and text presented in PK Summary and the

bioanalytical report in study VBRR0632 (Summary of lack of dose proportionality and exposure for mid dose is not aligned), i.e. the lack of increase in exposure between the mid and the high dose should be discussed.

Table 1: Summary of Toxicokinetic Parameters (Males and Females Combined) from bioanalytical report

Dose Level (µg/kg)	Day		C_{max} (ng/mL)	T_{max} (hr)	$AUC_{(0\text{-last})}$ (hr*ng/mL)
35	1	Mean	46.7	3.0	298
		SD	12.6	1.10	269
	22	Mean	0	0	0
		SD	0	0	0
175	1	Mean	336	3.80	4560
		SD	244	0.632	3110
	22	Mean	0	0	0
		SD	0	0	0
350	1	Mean	279	3.50	2810
		SD	117	1.08	1390
	22	Mean	0	0	0
		SD	0	0	0

Mean time for maximal plasma concentration was in the range of 3 to 3.6 hours, Half-life was not calculated as the study design with a gap between 4 and 24 hours did not allow for that. Due to large interindividual variation, gender differences could not be evaluated.

Distribution

Distribution studies designed to support the intravesical route of administration were not presented.

Instead, a literature study was submitted. This study was conducted by Di Paolo et al. and published in 2003 at the time, when VB4-845 was in Phase 1 for treatment of cancer in the head and neck.

To investigate the distribution of VB4-845 in mice, 6 µg of 99"'Tc-labeled VB4-845 specific radioactivity of 98.9 TBq/mmol) were diluted in a total volume of 150 µL of PBS and were injected i.v. into mice bearing established SW2 (expressing the target Ep-CAM) and COLO320 tumour xenografts (control tumour) at the contralateral flanks. Mice were sacrificed at different time points (10 min, 30 min, 1 h, 4 h, 16 h, 24 h, and 48 h) after treatment, and organs were removed to measure the accumulated radioactivity using a gamma counter. The amount of radioactivity/gram organ was given as percentage of the total injected dose, which was arbitrarily set to 100%.

After 48 hours VB4-845 show a tumour/blood ratio of 5.38. This is encouraging, however if tumour/liver or tumour/kidney ratio is considered, the ratios are 0.13 and 0.068, respectively.

Tumour/kidney ratios were at 10 min; 0.045, 30 min; 0.075, 1 hour; 0.073, 4 hours; 0.069, 16 hours; 0.068 and 24 hours; 0.086. This means that the amount in the kidney is between 22 and 13 times higher than in the tumour across the first 48 hours after an intravenous injection and that the clearance in kidney is as slow as in the tumour. Moreover, at 48 hours 16.5% of the dose was still retained in the kidney, 8.4% in the liver and 4.1% in spleen. It should also be noted that VB4-845 show only 2-3 times better binding to the Ep-CAM expressing tumour as compared to the control tumour across 1 to 48 hours after injection.

The following conclusion was presented for the cross-reactivity studies in human and chimpanzee tissues: In chimpanzee and human tissues, no VB4-845 binding over background levels was shown for brain, heart and striated muscle. Mild to moderate binding was observed on the surface and basement

membrane of epithelial cells in both human and chimpanzee kidney, skin and bladder at both 1.25 µg/mL and 5.0 µg/mL of VB4-845. Minimal to marked VB4-845 binding was also observed in both human and chimpanzee fallopian tube, pancreas, pituitary and liver.

Since the bladder is in direct contact with the kidney via ureter and retrograde flowbackflush from the bladder may occur as in bladder infections, a distribution study in rat using intravesical administration of radiolabeled VB4-845 should be submitted for assessment. The study should be designed to further investigate distribution to kidney, liver, spleen and bone marrow of VB4-845 in normal rats. Whether the study should be using single dose administration and/or repeat-dose administration should be justified by the timing of occurrence of kidney toxicity in patients, see MO on Pharmacokinetics programme. Further pharmacokinetic studies may be warranted, depending on the outcome of a distribution study using intravesical instillation.

Metabolism and Excretion

Metabolism of VB4-845 was not discussed and no studies submitted. Since VB4-845 is a chimeric protein with no unnatural amino acids and that it is anticipated that the product is cleared via urine after intra vesical instillation, this could be acceptable. However, in light of apparent systemic toxicity observed in patients in clinical trials, the short half-life of VB4-845 in the rat of 2.3 hours and the very long retention of radiolabelled VB4-845 in especially the kidney and liver in mice after intravenous administration, a thorough discussion of systemic metabolism and possible systemic clearance pathways of VB4-845 should be presented.

Pharmacokinetic drug interactions

Drug-drug interaction studies in Sprague-Dawley rats have been conducted to examine the potential effects of VB4-845 (s.c.) on the pharmacokinetics of certain anticancer agents (i.v. administration of paclitaxel, cisplatin and 5-FU) as well as any impact on VB4-845 (i.e., both victim drug and perpetrator drug liability) (VBI Report Nos. VBRR0315 and VBRR0319). VB4-845 had no impact on the pharmacokinetics on the other anticancer agents. When VB4-845 was co-administered with cisplastin, 5-FU or paclitaxel there was a significant decrease in the systemic exposure. The interaction effect on the exposure to VB4-845 was in the following order paclitaxel > 5-FU > cisplastin. The interaction with paclitaxel caused a > 90% decrease in systemic exposure to VB4-845. Pharmacokinetic drug interaction studies in rats indicate that the pharmacokinetic profile of oportuzumab monatox could change in combination with other chemotherapeutic agents (cisplatin, paclitaxel and 5-FU). The mechanism leading to the observed pharmacokinetic interaction together with the possibility of PK interaction with other drugs should be discussed, taking into account that clinical safety data suggest oportuzumab monatox can reach systemic circulation after intravesical administration in patients. Based on this discussion, the applicant should propose a wording for section 4.5 of SmPC.

However, it is agreed that for local administration of VB4-845 in the bladder, there would be no need to contraindicate the other drugs, provided that indeed the systemic exposure is negligible.

3.2.3. Toxicology

Species selection appear well justified. However, the applicant is requested for a discussion about the feasibility of using homologous product that binds to EpCAM protein in non-clinical species different to mice .

Single dose toxicity

RAT

A single dose toxicity study was conducted in rat using intradermal (i.d.) injection (VBRR0300, GLP except dose analysis).

In the dose-range finding study, i.d. injections of VB4-845 at doses of 1.14, 4.29. 8.57, 17.10, 42.90, and 85.70 µg/kg were administered. Skin swelling and red skin colour were observed at the injection site on Day 2 in rats treated ID. Otherwise, no adverse findings were observed (clinical signs, and changes in body weight and temperature, haematology, coagulation, clinical chemistry, and urinalysis). Necropsy was not performed.

Limited i.v. dosing was conducted in the dose-range finding study. I.v. injections of VB4-845 were investigated at doses of 429.00, 643.50, and 858.00 µg/kg. I.v. injections resulted in dose-dependent increases in some red blood cell parameters and in coagulation. Dose-dependent decreases in albumin (ALB) and total protein (TP) level and in albumin/globulin (A/G) ratio were also observed in these rats. However, the toxicological significance is unknown and probably not clinically relevant considering the high dose and route of administration.

Based on the results of the dose ranging study, i.d. injections of VB4-845 were given at doses of 4.61, 17.10, 42.90, and 85.70 µg/kg to assess the acute toxicity in rats. Injections were followed by a 14-day recovery period. During this time there was no evidence of systemic toxicity after the single intradermal injections of VB4-845 to Sprague Dawley rats at doses of 17.10, 42.90, and 85.70 µg/kg as compared to the control group injected with 20 mM Tris-500mM NaCl. Some treatment-related effects at the injection site were observed. Adverse skin related clinical signs such as slight to moderate skin swelling, red skin, thickening of skin, scabbing and crusting followed by scaring, skin scaling, etc. were observed at the dosing site of the single dose ID study animals following treatment. The incidence and the severity of these clinical signs increased with the dose level suggesting a strong dose dependent effect. These findings indicate poor local tolerance of VB4-845. However, for systemic toxicity, it is agreed that MTD was not reached.

MONKEY

No specific single dose toxicity study was conducted in monkey. Single dose toxicity was evaluated as part of the repeat-dose toxicity study using s.c. administration. See section 4.2.2.

Repeat-dose toxicity

RAT

VB4-845 was evaluated in a 7-day repeat-dose toxicity study using s.c. (1.0, 5.0, 35.0 and 77.8 µg/kg) and i.v. administration (only one dose level: 77.8 µg/kg/day). VB4-845 administered subcutaneously in doses up to 77.8 µg/kg showed no systemic toxicity and did not result in any mortality. Subcutaneous injections were found to elicit a localised irritation resulting in redness, oedema and lesions occurring in a dose-dependent manner. Histology evaluation described these lesions as fibrin-rich oedema in the dermis and subcutis, followed by necrosis of connective tissue and muscle in the deeper layers of the skin. Subsequently, ulceration, epidermal necrosis and regeneration of the overlaying skin was seen in the two higher dose groups. However, the extent of the skin reaction was limiting in that the symptoms at the injection site resolved or partly resolved over the course of the 14-day recovery period. NOAEL was set to the highest dose of 77.8 µg/kg/day based on lack of systemic toxicity. This is accepted. However, the clinical relevance of the skin lesions (e.g. local tolerance reactions) after s.c. administration occurring with dose-dependent severity should discussed and the lack of a repeat-dose toxicity study using intravesical administration should be justified.

When VB4-845 was injected intravenously it was capable of causing microvascular injury leading to pathologic sequalae consistent with vascular leak syndrome leading to high initial mortality. Histology

findings in animals dying after Day 8 were oedema and/or necrosis in the brain or heart and acute necrosis in the kidney. Findings after i.v. administration are considered of limited clinical relevance for an indication of intravesical instillation.

The study was conducted in 2003-2004 and claim to be GLP compliant according to FDA 21CFR, Part 58 and a comprehensive study inspection programme was listed. However, analysis of dosing solutions and bioanalysis are not complying to current standards. Analysis of the protein concentration of the dosing solutions indicated that there was less protein in the solutions than predicted, with the greatest loss occurring at the lowest doses. The bioanalytical method was not validated to current standards, see section 3.1.

MONKEY

The objective of the cynomolgus monkey study was to determine the maximum tolerated dose (MTD) of VB4-845 in an initial phase (Phase 1) using the subcutaneous route and to further investigate the toxicity, toxicokinetics and immunogenicity of VB4-845 following a weekly subcutaneous injection for 4 weeks followed by a 2-week recovery period in the cynomolgus monkey (Phase 2). In Phase 1, dose levels of 1 and 3.5 mg/kg in each of one male monkey was evaluated. In Phase 2, doses of 35, 175 and 350 µg/kg/week were evaluated in male and female monkeys (N=3, main, N=2, recovery).

The following conclusion was presented in the main study report: The once weekly administration of VB4-845 for 4 weeks produced localised skin lesions at the treatment sites that resulted in inconsequential microscopic changes (foci of minimal-slight chronic inflammation and/or hemorrhage), but no evidence of systemic inflammation was observed. Clinically, an increased incidence of skin flaking and skin redness was seen in all VB4-845-treated groups and yellow or blue discoloration of the skin was observed in a few animals given 175 or 350 µg/kg/day. In animals given 350 µg/kg/day, a higher incidence of brown material and skin lesions/blister at the treated site(s) were observed. A reduced appetite was noted more frequently in 350 µg/kg/day males and in 175 and 350 µg/kg/day females when compared to controls. In addition, increased alanine and aspartate aminotransferase values were observed in Female No. 452 given 350 µg/kg/day. Although these findings had no macroscopic or microscopic correlate, a relation to treatment cannot be totally excluded. Skin redness subsided during the recovery period and there were no treatment-related findings observed by the end of the recovery period. The no-observed adverse-effect level was determined to be 350 µg/kg/day. This is considered acceptable.

As discussed in section 3.2. a strong immune response was raised against VB4-845 from Day 14 and onwards resulting in complete lack of exposure on toxicokinetic Day 22. For further discussion on the immune response to VB4-845 in the monkey, refer to section 4.7.1. As mentioned in section 3.2, analysis of dosing solutions, revealed loss of study drug at the lowest dose level, resulting in the lowest dose being only 25-54% of the nominal dose (35 µg/mL). However, since the highest dose, 350 µg/kg/week is considered NOAEL, this has no implication for the conclusions of the study.

Genotoxicity

The omission of genotoxic evaluation is accepted, since VB4-845 is a fusion protein and not expected to interact with DNA.

Carcinogenicity

Evaluation of carcinogenic potential of VB4-845 was not conducted. Instead, a justification was presented. There is some evidence of risk of second primary malignancies developing in patients with primary bladder cancer, with a high likelihood in male patients (Sahin et al., 2016), however this seem not to be the case for VB4-845 in clinical trials. This is discussed further in the Clinical Safety report. In

this particular case with a fusion protein instilled into the bladder, no new animal studies of carcinogenic potential should be required. However, consistent with ICH S6 guidance, the risk of inducing secondary cancers should be further discussed based on a review of clinical and non-clinical data with exotoxin A or other immunotoxins.

Reproductive and developmental toxicity

No evaluation of the reproductive toxicity potential of VB4-845 was submitted. Instead a justification for not doing so was presented.

Ninety percent of new bladder cancer diagnoses in the US occur in people age 55 years or older with an average age of diagnosis being 73 years, which is usually post-menopausal age (Saginala et al., 2020). Hence, based on the epidemiology of bladder cancer, it is highly unlikely that VB4-845 will have any embryo-foetal effects in women or have detrimental effects on male fertility. Moreover, in section 4.6 of SmPC, the following wording is included:

Pregnancy

There are no or limited amount of data from the use of oportuzumab monatox in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3).

Based on the mechanism of action, oportuzumab monatox may cause foetal harm when administered to a pregnant woman.

Oportuzumab monatox should not be used during pregnancy unless the clinical condition of the woman requires treatment with Oportuzumab Monatox.

Women of childbearing potential have to use effective contraception during treatment and up to six months after treatment.

Male patients with female partners of reproductive potential have to use effective contraception during treatment with oportuzumab monatox and for three months after the last dose.

Breast-feeding

It is unknown whether oportuzumab monatox or oportuzumab monatox metabolites are excreted in human milk.

A risk to the newborns/infants cannot be excluded.

Breast-feeding should be discontinued during treatment with oportuzumab monatox.

Fertility

In males, it has been demonstrated that administration of a relatively low dose of ETA (a portion of ETA is a component of oportuzumab monatox) is capable of impairing fertility (see section 5.3).

The potential for reproductive toxicity of VB4-845 is unknown. Literature studies indicate that the ETA portion of the molecule may be toxic to reproduction. However, since i) VB4-845 is intended for intravesical instillation only, ii) very limited systemic exposure is observed, iii) the intended population is largely elderly men and post-menopausal women (which according to ICH S5 could justify omission of DART studies) and that iiii) adequate precautionary measures are described in SmPC, nonclinical reproductive toxicity evaluation of VB4-845 is not warranted.

Local tolerance

A local tolerance study of VB4-845 in the bladder has not been performed. Although principally, stand-alone local tolerance studies are not warranted, if local tolerance endpoints can be included in repeat-dose studies. applicant state that, since VB4-845 shows poor cross reactivity to rat tissue, results may be misleading. This is acknowledged, although rather severe toxicity to tissues in animals not expressing Ep-CAM is observed. Clinical data may suffice at this stage of development. However, the mechanism of action and the possible resulting tissue damage to the lining of the bladder (not tumour tissue) should be discussed as to further justify the lack of a local tolerance study in rat using intravesical instillation.

Other toxicity studies

Di Paolo et al., 2003 published a study on effects of i.v. administration of VB4-845 in mice. Apart from *in vitro* and *in vivo* tumour pharmacology, the study also included biodistribution (see section 3.3) and *in vivo* toxicity testing. Toxicity of the immunotoxin was determined in C57BL/6 mice after repeated injections of escalating doses of VB4-845 given every other day for three cycles (0.25 mg/kg and 0.50 mg/ dose) or for two cycles (1 mg/kg dose). VB4-845 did not affect liver enzymes at repeated doses of 0.25 or 0.5 mg/kg in immunocompetent mice. Elevated transaminase activity (ALT/AST) was associated with moderate hepatocyte necrosis after two i.v. injections of 1.0 mg/kg of VB4-845. Given rare incidents of hepatotoxicity in clinical trials despite only local administration into the bladder combined with limited systemic absorption, a thorough discussion of the mechanism behind and clinical relevance of hepatotoxicity observed in mice should be presented.

Antigenicity

RAT

VB4-845 was administered subcutaneously at doses of 0, 1, 5, 35 and 77.8 µg/mL every day for 7 day in rats. Another group of animals received 77.8 µg/mL of VB4-845 intravenously as in the 7 Day toxicity study (VBRR0301). Blood samples were collected on Day 21 to monitor the anti-VB4-845 immune response by enzyme linked immunosorbent assay (ELISA) in rat serum. Antigenicity was determined to intact VB4-845 and the 4D5 single chain variable fragment (scFv) or Pseudomonas exotoxin (PE) portions of VB4-845 [VBRR0280].

After s.c. administration of VB4-845, a substantial immune response was observed on Day 21 even at the low dose level (5 µg/kg). At the highest dose (77.8 µg/kg), the increase in antibody titre tended to be less dramatic and in one case even decreased, suggesting that antibodies may be forming immune complexes with VB4-845. applicant state that this could prevent detection of VB4-845-specific antibodies by ELISA, since these complexes are rapidly cleared from circulation, thus lowering the concentration of free antibody. The study demonstrated that the PE component of VB4-845 was the most antigenic portion of the molecule. There was only a moderate immune response observed in rats when VB4-845 was injected i.v. as compared to s.c. administration. This may be explained by the rapid clearance of VB4-845 (half-life ~2.3 hours), preventing the molecule from reaching the lymphoid organs to initiate an immune response. Since antigenicity was only determined at one time point namely Day 21, it is not known whether toxicokinetics was impacted by antidrug antibodies on Day 7 in study VBRR0301.

MONKEY

Plasma samples were taken from all study animals in the repeat-dose toxicity study (VBRR0632) on Day 0 and prior to dosing on Days 7, 14, 28, and at the end of the recovery period (Day 42) to determine the antibody response induced in Cynomolgus monkeys by VB4-8452. Day 0 samples were not analysed on account of lack of drug exposure and as a result, the absence of antibody titre. This

was confirmed in Day 7 plasma sample results, where antibodies titres were either below or near the limit of detection. Hence all animals appeared to be ETA naïve. Plasma samples taken on Day 7 with no anti-VB4-845 titres were not analysed further for anti-ETA or anti-4D5 titres.

Antibody titres peaked between Days 14 and 28, depending on dose group. As the dose level of VB4-845 increased, there was a corresponding increase in immune response as seen on Day 28. Examination of the two components of VB4-845 indicated that the majority of the immune response was directed towards the ETA portion.

Repeated subcutaneous administration of VB4-845 in Cynomolgus monkeys elicited an immune response, which also included neutralising antibodies. Neutralising antibodies were not detectable until after two doses of VB4-845 (Day 14), and titres decreased upon the completion of dosing. The development of neutralising antibodies did not appear to be dose dependent.

As expected both rat and monkey raised antidrug antibodies against VB4-845, a human/bacterial fusion protein. Low but measurable pre-existent anti-exotoxin A (ETA) (252-608) antibodies were detected in 86.2% of patients prior to drug administration in study 3. It is known that systemic exposure to ETA elicits an immune response in humans (SmPC). However, pre-existing ETA immunity appear not to have been observed in the rat and monkey repeat-dose studies.

Immunotoxicity

Omission of a discussion of immunotoxicity should be justified.

3.2.4. Ecotoxicity/environmental risk assessment

Since VB4-845 is a fusion protein of an antibody fragment and pseudomonas exotoxin without the cell binding domain linked with natural amino acids, VB4-845 is considered a natural product of low stability and no further studies will be required to investigate any potential risk to the environment.

3.2.5. Discussion on non-clinical aspects

Pharmacology

VB4-845 is a recombinant fusion protein consisting of a tumour-targeting, humanised, anti-epithelial cell adhesion molecule (EpCAM) single-chain antibody fragment genetically linked to the truncated form of Pseudomonas exotoxin A (ETA252-608) that lacks the cell binding domain.

VB4-845 is believed to act through a dual mechanism of action. The first involves toxin-mediated killing following the specific binding and internalisation of VB4-845 to EpCAM overexpressed on the tumour cell surface resulting in inhibition of protein synthesis and ultimately apoptotic cell death. The second mechanism is believed to involve the development of an adaptive T cell-mediated anti-cancer response subsequent to the appearance of immunogenic cell death (ICD) markers elicited during VB4-845 tumour cell killing. Proof of concept of these the dual mechanism of action is considered established from both *in vitro* and *in vivo* studies. However, one *in vitro* study indicates that VB4-845 binds to normal kidneys cells at a similar potency as to a kidney tumour cell line. This is a concern since cross reactivity studies also showed moderate binding to kidney tissues and kidney toxicity was observed in the clinical setting.

Several *in vivo* studies were presented showing reduction in tumour size, during treatment with VB4-845. One study of peri-tumoural injection was not sufficiently detailed in the report, e.g. missing raw data on the control group. Deficiencies should be clarified.

Safety pharmacology was evaluated in the monkey repeat-dose toxicity study. In principle this strategy is considered acceptable, but since timing of the neurological evaluation were performed at a time of no systemic exposure and that respiratory safety was not evaluated, the safety pharmacology assessment is deemed insufficient.

Pharmacokinetics

Evaluation of pharmacokinetics of VB4-845 is limited. It is acknowledged that the nonclinical studies at least on Day 1 provide higher systemic exposure than apparently observed in the clinical setting, however this may not support investigation of systemic adverse events observed in the clinical studies (gastrointestinal toxicity, nephrotoxicity, hepatotoxicity and elevated platelet levels). Moreover, lack of GLP compliance of bioanalysis and documentation of systemic exposure beyond Day 1 of the general toxicity study in monkey (toxicokinetics) due to neutralising antidrug antibodies triggers a general concern on the nonclinical pharmacokinetic programme, since patients are exposed for up to 12 weeks, and obviously animal models did not show sufficient exposure to cover this treatment period in the clinical setting. As a first step in the characterisation of the systemic safety profile of oportuzumab monatox after intravesical administration, the possibility for systemic absorption after intravesical instillation of VB4-845 should be investigated from the clinical point of view (see clinical safety MO). In addition, the applicant is asked for a thorough discussion of the mechanism behind and clinical relevance of renal and hepatic toxicities, as well as for the elevated platelet levels, observed in the nonclinical and clinical studies. If the risks cannot be adequately characterised by these both approaches, a new distribution study using radiolabelled VB4-845 installed into the bladder of rats should be performed. Whether the study should include both single and repeat-dose should be thoroughly justified, i.e. be in line with timing of findings in the clinical setting.

Metabolism and excretion were not evaluated for VB4-845. This could in principle be acceptable if systemic absorption from the bladder was negligible as it probably is in most cases. However, some tissue distribution from the bladder may occur as indicated from the list of adverse effects (SmPC). Moreover, there are discrepancies between the systemic half-life of non-radiolabelled VB4-845 in rat and radiolabelled VB4-845 in kidney and liver tissues after intravenous administration. Therefore, possible clearance pathways of VB4-845 should be further discussed.

Toxicology

The evaluation of potential toxicity after intravesical instillation is not deemed sufficient. Studies using subcutaneous administration show dose dependent severity of skin tissue damage after repeat-dose administration in both rat and monkey. In light of missing local tolerance studies after intravesical instillation, the relevance of these findings in EpCAM negative tissues to the normal lining of bladder should be further discussed including the mechanism of action. Moreover, the omission of presenting toxicity studies using a clinically relevant route of administration should be further justified. Liver toxicity was observed in mice after intravenous administration and since rare incidents of liver toxicity were observed in the clinic, this should also be further elaborated upon.

3.2.6. Conclusion on non-clinical aspects

From a non-clinical perspective, VB4-845 can be approvable, provided that the several other concerns raised on deficiencies identified in both Pharmacology, Pharmacokinetics and Toxicology sections are addressed satisfactorily.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Overview of the Clinical Trials Providing Safety and Efficacy Data for VB4-845:

Study No.	Status	Title	Study Description	No. Enrolled/Completed[1]	Doses and Dosing Regimen
Phase 1/2 VB4-845-02-I Kowalski et al., 2010	Completed	A Phase I/II Open Label Study to Evaluate the Safety and Tolerability of VICINIUM (VB4-845) in Subjects with Superficial Refractory or BCG-Intolerant Transitional Cell Carcinoma (TCC) of the Bladder	Open-label, multicenter, dose escalating study of intravesical VB4-845 administered to patients with BCG refractory or intolerant TCC (urothelial carcinoma) of the bladder (Phase 1) followed by a multi-center, open- label, safety, tolerability and efficacy evaluation of the recommended dose of VB4-845 as determined in Phase 1 (Phase 2).	64/63	0.10, 0.20, 0.33, 0.66, 1.32, 2.64, 5.28, 10.56, 13.73, 17.85, 23.20, or 30.16 mg once weekly for 6 weeks
Phase 2 VB4-845-02-IIA Kowalski et al., 2012	Completed	Phase 2 Study to Evaluate the Efficacy and Tolerability of Intravesical VICINIUM in Patients with Non-Invasive Urothelial CIS Previously Treated with BCG	Phase 2, single treatment arm, dual-treatment schedule, open-label, non-randomized study in subjects with EpCAM-positive, non-invasive urothelial CIS with or without non-invasive papillary disease, who failed or were intolerant to previous treatment with BCG therapy.	46/45 mITT 45	Treatment Schedule A: Induction phase-30 mg once weekly for 6 weeks, followed by 6 weeks of no therapy. Maintenance phase- 30 mg once weekly for 3 weeks followed by 9 weeks of no therapy (repeated up to a year). Treatment Schedule B: Same as Treatment Schedule A, except the induction phase consisted of 12 weekly treatments.
Phase 3 VB4-845-02-IIIA	Ongoing	An Open Label, Multicenter, Phase 3 Study to Evaluate the Efficacy and Tolerability of Intravesical VICINIUM in Subjects with Non-Muscle-Invasive CIS and /or High-Grade Papillary Disease of the Bladder Previously Treated with BCG	Phase 3, open-label, non-randomized, multicenter study in subjects with NMIBC that is refractory to or relapsed following adequate BCG treatment defined as at least 2 courses of full dose BCG. Eligible subjects must have histologically confirmed high-grade Ta, any-grade T1 or CIS (with or without associated papillary disease).	133/14 mITT 133[2]	Induction phase: Subjects receive twice weekly (BIW) dosing for 6 weeks followed by once weekly dosing for 6 weeks, i.e., 18 doses over 12 weeks. Maintenance phase: Subjects eligible to enter the maintenance phase are treated every other week. Total treatment (Induction + Maintenance) is up to 104 weeks (2 years).

Abbreviations: BCG=Bacillus Calmette-Guerin; CIS=carcinoma in situ; mITT=modified intent-to-treat
[1]For the Phase 3 trial, completed subjects corresponds to those that have reached end of study (24 months).
[2]Safety dataset from the ongoing Phase 3 study includes all enrolled subjects

3.3.1. Pharmacokinetics

Cell based biopharmaceutical methods for the quantification of VB4-845 in human plasma and ELISA assays for determination of immunogenicity towards VB4-845, the ETA and scFv components were developed and validated. No pharmacokinetic data analysis was conducted. No pharmacokinetic models were applied. No statistical analyses related to PK were conducted.

The applicant states that intravesical administration of oportuzumab does not result in systemic exposure.

No pharmacokinetic parameters have therefore been derived from any of the trials and only a very small number of concentrations above the assay LLOQ were detected. A total of 4 quantifiable samples (in 3 individual subjects) were measurable across a total of 174 subjects based on the two trials completed to date and these were marginally above the assay lower limit (< 2-fold) or LLOQ (Table 2, below).

Table 2: PK Samples Above the LLOQ

Study	Subject	Timepoint	Value (pg/mL)	LLOQ (pg/mL)
VB4-845-02-I	47	Day 1, 1h post-dose	19	14
VB4-845-02-I	47	Day 8	17	14
VB4-845-02-I	60	Day 1, 1h post-dose	18	14
VB4-845-02-IIIA	1420002	Week 6 Dose 2	3228.4	1700

According to the applicant, the Phase 1/2 and Phase 3 PK analyses demonstrate that intravesical administration of oportuzumab does not result in systemic exposure.

Formal comparison between patient populations has not been conducted because no pharmacokinetic parameters have been derived from any of the trials and only a very small number of concentrations above the assay LLOQ were detected. In addition, no PK data in patients with renal or hepatic impairment has been presented.

Oportuzumab has not been studied in children.

No drug-drug interaction studies have been conducted, as none is expected due to the local administration of the molecule resulting in little to no exposure in subjects based on observed data in subjects.

No exposure-safety data has been presented. The applicant argues that due to intravesical administration the risk of vascular leak syndrome (VLS) is minimal.

3.3.2. Pharmacodynamics

VB4-845 has a dual mechanism of action that consists of a well-defined, antibody-directed cytotoxic effect that promotes a cell-mediated, anti-tumour immune response. The first mechanism involves cytotoxicity against both rapidly proliferating cancer cells as well as slowly dividing or quiescent cancer stem-like cells and is not susceptible to multi-drug resistance. The second mechanism is believed to involve the promotion of a cell-mediated anti-tumour immune response subsequent to the appearance of immunogenic cell death (ICD) biomarkers elicited during VB4-845 tumour cell killing.

According to the inclusion criteria for enrolment in the Phase 1/2 and Phase 2 VB4-845 studies, subjects were required to have a histologically confirmed diagnosis of refractory grade 2 or grade 3 Ta, T1 or Tis TCC of the bladder and evidence of EpCAM expression on the tumour cell membrane.

Study VB4-845-02-I (Phase 1/2 Study)

Anti-Drug Antibody (ADA, Anti-VB4-845) Responses

Plasma samples from 63 subjects participating in the Phase 1/2 study were analysed for anti-VB4-845 antibodies. Thirty percent of subjects (19/63) had measurable ADA titres by week 2 following VB4-845 administration. Despite VB4-845 not being detectable in the circulating blood or systemic circulation, an immune response against VB4-845 was detected in 54/61 (89%) subjects by their final visit (Week 10-12).

Anti-ETA Antibody (HATA) Responses

At pre-dose, 46/63 (73%) subjects had relatively low but measurable anti-ETA antibodies. Anti-ETA antibodies were detectable in 47/61 (77%) subjects by the end of the study Nineteen percent (12/63) had measurable HATA titres at Week 2. The highest titre of 724,436 was observed at Week 5 in one subject. This same subject demonstrated a complete response.

Anti-4D5MOCB Antibody (HAHA) Responses

Following VB4-845 treatment anti-4D5MOCB antibodies were observed in 10/61 (16%) subjects by the final visit (Week 10-12). HAHA titres ranged from <1,000 to 15,900, with most subjects showing titres <1,000 (with 1,000 being the limit of detection). The highest observed titre of 15,900 occurred on Week 5 in one subject (same subject with the highest HATA titre) dosed at 17.85 mg. Twenty-one (33%) subjects had measurable HAHA titres pre-dose, with the highest titre being 8,000.

Most subjects had pre-existing anti-ETA, likely reflecting previous exposure to Pseudomonas spp and accounts for the majority of the immunogenicity seen pre-study based on both assays at baseline. The boosted immune response based on the final measurement is mainly against the ETA component with minimal to no antibodies directed towards the 4D5MOCB part of molecule.

There was a trend towards a lower median ADA titre in the lowest dose group (0.1 to 1.0 mg), although the maximum observed titres were comparable across dose groups.

Anti-Drug Antibody (Anti-VB4-845) Titre and Assessment of Impact on the Efficacy Response

Most subjects (71%) had low, but measurable baseline anti-VB4-845 and anti-ETA antibodies. An analysis was conducted to determine if the efficacy of VB4-845 differed between those subjects who had baseline titres and those who did not. There was no difference between the response rates of the two groups. Similar results were seen at the final visit (10-12 weeks).

Table 3: Response Rates for Bladder Cancer Subjects Who Were ADA Positive or Negative at Baseline

Response	ADA-Positive	ADA-Negative
Complete or Partial Response	66.7% (26/39)	64.3% (9/14)
Stable Disease	17.9% (7/39)	21.4% (3/14)
Progression	15.4% (6/39)	14.3% (2/14)

Abbreviations: ADA=anti-drug antibody

Table 4: Response Rates for Bladder Cancer Subjects Who Were ADA Positive or Negative at Final Visit

Response	ADA-Positive	ADA-Negative
Complete or Partial Response	69.6% (32/46)	50.0% (3/6)
Stable Disease	17.4% (8/46)	16.7% (1/16)
Progression	13.0% (6/46)	33.3% (2/6)

Abbreviations: ADA=anti-drug antibody

Study VB4-845-02-IIIA (Phase 3 Study): (SBR0889 Rev 01)

In CIS subjects, the presence of baseline ADA or NAb did not influence the clinical outcome. There were no major differences in the CR rates between subjects that were positive or negative for the presence of baseline ADA, the baseline ADA titres, and the presence of neutralising activity of the baseline ADA. In addition, no change in the CR rate was observed as a function of the strength of the post-treatment ADA response. Furthermore, there was no observed difference in duration of response

(DoR) for efficacy between subjects who were positive or negative for ADA at baseline, or the strength of the baseline and post-treatment ADA titre. However, there was a slight imbalance between groups and number of subjects in some subgroups was small.

Table 5: Complete Response Rate by Baseline ADA Status and Titer

Time Point	All CIS	Baseline ADA Status		Baseline ADA Titer		
		Positive	Negative	<500	500-<10,000	≥10,000
3 months	36/93 (39%)	30/68 (44%)	2/9 (22%)	7/25 (28%)	12/28 (43%)	13/24 (54%)
6 months	25/93 (27%)	22/68 (32%)	1/9 (11%)	5/25 (20%)	10/28 (36%)	8/24 (33%)
9 months	19/93 (20%)	16/68 (24%)	1/9 (11%)	4/25 (16%)	7/28 (25%)	6/24 (25%)
12 months	15/93 (16%)	13/68 (19%)	0/9 (0%)	2/25 (8%)	6/28 (21%)	5/24 (21%)

Abbreviations: ADA=anti-drug antibody; CIS=carcinoma in situ

Table 6: Complete Response Rate by Baseline Neutralising Antibody

Timepoint	All CIS	Baseline Neutralizing Antibody Status	
		Positive	Negative
3 months	36/93 (39%)	24/51 (47%)	8/26 (31%)
6 months	25/93 (27%)	18/51 (35%)	5/26 (19%)
9 months	19/93 (20%)	14/51 (27%)	3/26 (12%)
12 months	15/93 (16%)	11/51 (22%)	2/26 (8%)

Abbreviations: CIS=carcinoma in situ

Table 7: Complete Response Rate by Highest Post-Treatment ADA Titer

Time Point	All CIS	Highest Post-treatment ADA Titer		
		<500,000	500,000-<2,000,000	≥2,000,000
3 months	36/93 (39%)	6/23 (26%)	14/27 (52%)	11/19 (58%)
6 months	25/93 (27%)	4/23 (17%)	12/27 (44%)	6/19 (32%)
9 months	19/93 (20%)	3/23 (13%)	8/27 (30%)	5/19 (26%)
12 months	15/93 (16%)	3/23 (13%)	7/27 (26%)	3/19 (16%)

Abbreviations: ADA=anti-drug antibody; CIS=carcinoma in situ

Table 8: Recurrence Free Rates by Baseline ADA Status and Titer

Time Point	All Papillary	Baseline ADA Status		Baseline ADA Titer		
		Positive	Negative	<500	500-<10,000	≥10,000
3 months	27/40 (68%)	21/30 (70%)	2/2 (100%)	7/9 (78%)	7/12 (58%)	9/11 (82%)
6 months	22/40 (55%)	17/30 (57%)	1/2 (50%)	5/9 (56%)	5/12 (42%)	8/11 (73%)
9 months	17/40 (43%)	12/30 (40%)	1/2 (50%)	4/9 (44%)	4/12 (33%)	5/11 (45%)
12 months	16/40 (40%)	11/30 (37%)	1/2 (50%)	4/9 (44%)	4/12 (33%)	4/11 (36%)

Abbreviations: ADA=anti-drug antibody

Table 9: Recurrence-Free Rates by Baseline Neutralising Antibody Status

Time Point	All Papillary	Baseline Neutralizing Antibody Status	
		Positive	Negative
3 months	27/40 (68%)	17/24 (71%)	6/8 (75%)
6 months	22/40 (55%)	15/24 (63%)	3/8 (38%)
9 months	17/40 (43%)	11/24 (46%)	2/8 (25%)
12 months	16/40 (40%)	10/24 (42%)	2/8 (25%)

Table 10: Recurrence-Free Rates by Highest Post Treatment ADA Titer

	All Pap	Highest Post-treatment ADA Titer		
Time Point		<500,000	500,000-<2,000,000	≥2,000,000
3 months	27/40 (68%)	6/7 (86%)	6/7 (86%)	11/12 (92%)
6 months	22/40 (55%)	4/7 (57%)	6/7 (86%)	8/12 (75%)
9 months	17/40 (43%)	3/7 (43%)	5/7 (71%)	5/12 (42%)
12 months	16/40 (40%)	3/7 (43%)	4/7 (57%)	5/12 (42%)

Abbreviations: ADA=anti-drug antibody

Furthermore, the presence of baseline ADA and NAb, or baseline or post-treatment ADA titres did not impact efficacy in subjects with papillary disease. There were no major differences in recurrence-free rates between subjects that were positive or negative for the presence of baseline ADA, the strength of the baseline ADA titre, the presence or absence of neutralising activity of the baseline ADA or the strength of the post-treatment ADA response.

Table 3 (above) provides a comparison of the ADA-status and response, but no statistical assessment has been provided. Additionally, and although numbers are small, it is confounding that ADA-positive patients at the end of treatment appear to have a higher CR rate and lower progression rates than ADA-negative subjects (Table 4; a typo is identified in the ADA-negative/stable disease row where it seems that the correct figure would be '1/6' and not '1/16'). The same applies when looking at tables 8, 9 and 10 (CIS patients) and 12, 13 and 14 (papillary patients) as efficacy seems to be related to ADA- and/or NAb-positive status, as CR and recurrence-free rates are higher for positive patients, which is contradictory. In this sense, the applicant should clarify whether (i) a local immunogenicity process occurs in the bladder and ADA are able to escape to systemic circulation; or (ii) a fraction of the locally administered dose escapes from the bladder to systemic circulation, which could represent a higher relevant fraction at higher doses, resulting in a systemic immunogenicity process. DoR is difficult to relate to ADA or Nab status, as NAb-patients at baseline have longer DoR (287 days) than NAb-negative (155 days).

The same applies when looking at tables 8, 9 and 10 (CIS patients) and 12, 13 and 14 (papillary patients) as efficacy seems to be related to ADA- and/or NAb-positive status, as CR and recurrence-free rates are higher for positive patients, which is contradictory. In this sense, the applicant should clarify whether (i) a local immunogenicity process occurs in the bladder and ADA are able to escape to systemic circulation; or (ii) a fraction of the locally administered dose escapes from the bladder to systemic circulation, which could represent a higher relevant fraction at higher doses, resulting in a systemic immunogenicity process. DoR is difficult to relate to ADA or Nab status, as NAb-patients at baseline have longer DoR (287 days) than NAb-negative (155 days).

Impact of ADA and NAb on Safety

The percentage of subjects experiencing any TEAE was 93% (91/98) and 73% (8/11) for baseline ADA-positive and baseline ADA-negative subjects, respectively. There is a statistically significant difference (p=0.03) in the frequencies of TEAEs between these two subgroups.

The potential impact of baseline ADA and titre and baseline NAb on serious AEs (SAEs) was also analysed. The percentage of subjects who experienced SAEs who were baseline ADA-positive and ADA-negative were 17% (17/98) and 9% (1/11), respectively.

The effect of post-treatment ADA titre was analysed to determine the impact on safety. When comparing all TEAEs as a function of the highest post-treatment ADA titre, the percentage of subjects in each of the three groups of ADA titre <500,000, between 500,000 and 2,000,000 and ≥2,000,000

was found to be 80% (24/30), 91% (31/34) and 97% (30/31), respectively, with a significant difference observed between the highest and the lowest titre subgroups (p=0.04). The percentage of treatment-related TEAEs for the three titre subgroups were 53% (16/30), 47% (16/34) and 65% (20/31), respectively and were not significantly different. The percentage of subjects experiencing SAEs in the ADA titre group with ≥2,000,000 (29%; 9/31) was significantly different than the <500,000 and 500,000 to 2,000,000 titre subgroups which were 7% (2/30) (p=0.03), and 9% (3/34) (p=0.04), respectively.

Screening of Bladder Tumour Tissue Biopsies for EpCAM Expression

In the Phase 1/2 study, 73 of 75 (>97%) tumour biopsies from subjects screened for EpCAM expression, were found to be positive. Sixty-four of these subjects were enrolled in the study. Most subjects, 61% (39/64) exhibited high (3+) expression of EpCAM. Moderate and low expression was exhibited in 33% (21/64) and 6% (4/64) of biopsy samples, respectively.

In the Phase 2 VB4-845 study, 46 subjects with EpCAM positive tumours were enrolled. Forty-five subjects were in the modified intent-to-treat (mITT) population, and were analysed for efficacy, with 22 in Treatment Schedule A (Cohort 1) and 23 in Treatment Schedule B (Cohort 2). The complete response rate for Cohort 1 and Cohort 2 was 50% and 39%, respectively, with a total of 44% across the two cohorts. In both cohorts, the majority of the subjects had a 3+ EpCAM expression score with 72.7% of subjects in Cohort 1 and 75.6% of subjects in Cohort 2 scoring 3+.

The data was further analysed to determine if there was a correlation between EpCAM expression status and the ability to achieve a complete response. A complete response at 3 or 6 months was achieved in 44.4% (20/45) of the subjects. The ability to achieve a complete response was similar for subjects with 2+ (44.4%) or 3+ (44.1%) EpCAM scores. Of the 2 subjects with a 1+ EpCAM score, one was a complete responder.

There was no apparent correlation between the ability to achieve a complete response and the percentage of tumour cells with 3+ EpCAM staining. Similarly, there was no clear correlation between percentage of subjects achieving a complete response and the percentage of total cells demonstrating any level of positive EpCAM staining.

The Phase 3 study enrolled 133 subjects with BCG-unresponsive NMIBC - CIS, high-grade Ta or any grade T1 papillary disease or CIS plus papillary disease who failed previous treatment with BCG. In this study a total of 93 subjects had baseline screening biopsy samples that were retrospectively evaluated for EpCAM expression by IHC. In addition, 45 subjects who had treatment failure had biopsy samples that were evaluated post-treatment.

As in the previous trials, the majority of the subjects demonstrated baseline EpCAM scores of high (3+) to moderate (2+) levels of staining intensity. EpCAM screening showed that 37 of 93 (39.8%) and 38 of 93 (40.9%) subjects exhibited high/strong (3+) and moderate (2+) membrane staining, respectively. Only 16 of 93 (17.2%) subjects exhibited weak (1+) staining, while 2 of 93 (2.2%) subjects' screening tumours were negative for EpCAM (score of 0). The EpCAM expression data were evaluated to determine if there was a correlation between EpCAM expression and VB4-845 efficacy. The data demonstrate that there is no correlation between baseline EpCAM expression level and disease-free status at 3 months.

Additional analysis of EpCAM expression was conducted in the Phase 3 (VB4 845 02 IIIA) study, focusing on potential correlation between EpCAM expression and efficacy and treatment failure. Additional analyses of EpCAM expression by percent of cells staining positive, and percent staining with 3+ EpCAM intensity, were compared with disease-free status at 3 months.

Analysis of the correlation of the overall baseline EpCAM score and the complete response rate at different time points or the duration of response for CIS subjects demonstrated that there is no association between efficacy response and baseline EpCAM expression.

Of the 93 subjects with screening biopsy evaluations, 45 of 93 (48.4%) were disease-free (CIS subjects with a complete response and T1/Ta subjects without recurrence) after 3 months of treatment with VB4-845. Disease-free rates were 56.3%, 36.8% and 54.1% for subjects with 1+, 2+, or 3+ EpCAM scores, respectively.

there was no association between the intensity of EpCAM expression or the proportion of EpCAM-positive cells and the ability to respond to VB4-845.

In addition to screening biopsy specimens, final biopsy specimens were analysed for membrane EpCAM expression in 45 subjects who failed treatment. Most of the final biopsy samples displayed strong or moderate EpCAM staining. Of the 45 subjects with final timepoint biopsies, 15 of 45 (33.3%) exhibited strong (3+) staining, 28 of 45 (62.2%) exhibited moderate (2+) staining and 2 of 45 (4.0%) exhibited weak (1+) staining.

For treatment failure subjects in which both screening and final EpCAM evaluations were available, no consistent difference in staining intensity was observed between the two timepoints.

Pharmacodynamic interactions with other medicinal products or substances

Studies on pharmacodynamic interactions with other medicinal products or substances has not been presented. The applicant is asked to clarify whether any of the enrolled patients in the pivotal studies received concomitant medicines that could have pharmacodynamic interactions with VB4-845. In addition, the applicant is asked to discuss any potential pharmacodynamic interactions with other medicinal products or substances, e.g. described in the literature.

Genetic differences in PD response

Studies on genetic differences in PD response has not been presented. The applicant is asked to discuss whether genetic differences in PD response to VB4-845 may occur, e.g. described in the literature.

Relationship between plasma concentration and effect

There is an apparent dose-dependent clinical response, relating the amount of VB4-845 placed into the bladder (directly and accumulated over treatment) and CR and/or tumour progression. The RP2D and Phase 3 dose selection is endorsed as the higher dose range (≥ 10 mg) reveals higher rates of CR and less tumour progression. Since the dose recommendation has been established at 30 mg and roughly 50% of the patients were included in the group of ≥10 mg, the applicant is encouraged to provide the Clinical Response analysis stratified by the dose levels above 10 mg.

No information was provided regarding the exposure-safety analysis in order to understand whether any significant relationship was present.

Phase 1/2 and Phase 3 PK analyses demonstrate that intravesical administration of VB4-845 does not result in systemic exposure. Therefore, no thorough QT/QTc study was conducted. However, electrocardiogram (ECG) measurements were conducted in the clinical studies.

The applicant is asked to describe the ECG measurements of the subjects with detectable systemic concentrations of VB4-845.

3.3.3. Discussion on clinical pharmacology

Pharmacokinetics

VB4-845 has been studied in three clinical trials.

Cell based methods were used for quantification of VB4-845 in human plasma. Cross-validation between methods is requested. ELISA assays were used for determination of immunogenicity towards VB4-845, the ETA and scFv components. A less sensitive assay was used to quantity samples from the Phase 3 trial. Validation report (CIR19123) should be submitted. The bioanalytical reports of sample analysis including immunogenicity measurements conducted in clinical studies VBRR0400, VB-845-02-I and IIIA should be submitted. Results of ongoing long-term stability studies should be submitted when available.

No systemic exposure of VB4-845 was observed except for 4 samples with detectable results. The applicant suggest that the 4 sample results >LLOQ are assay artefacts and thus false positive results. No pharmacokinetic parameters could be derived.

No other specific clinical pharmacology trials have been conducted to assess risk in renally or hepatically impaired patients because VB4-845 is not exposed systemically and drug exposure is confined to the bladder and tumour.

Pharmacodynamics and Pharmacokinetics-Pharmacodynamics (PK/PD)

According to the inclusion criteria for enrolment in the Phase 1/2 and Phase 2 VB4-845 studies, subjects were required to have a histologically confirmed diagnosis of refractory grade 2 or grade 3 Ta, T1 or Tis TCC of the bladder and evidence of EpCAM expression on the tumour cell membrane. The applicant is asked to clarify whether VB4-845 treatment should exclusively be targeted patients with histologically confirmed diagnosis of refractory grade 2 or grade 3 Ta, T1 or Tis TCC of the bladder and evidence of EpCAM expression on the tumour cell membrane.

In the Phase 3 study, all post-baseline samples tested were positive for anti-VB4-845 ADA; for most subjects, the most immunogenic portion of VB4-845 was the ETA (252-608) portion of the molecule as compared to the humanised 4D5MOCB scFv.

Immunogenicity (confirmation, binding strength, characterisation, and neutralisation) was measured pre-dose administration and at intervals during treatment, end of treatment and follow up. VB4-845 is a scFv platform containing a sequence derived from ETA and, therefore, a high proportion of subjects had pre-existing antibodies directed towards the ETA component of the molecule.

The strength of the baseline ADA and treatment-boosted ADA titre did not appear to have an impact on efficacy signals.

The percentage of subjects experiencing any TEAE was 93% (91/98) and 73% (8/11) for baseline ADA-positive and baseline ADA-negative subjects, respectively in the frequencies of TEAEs between the two subgroups (p=0.03). The percentage of subjects who experienced SAEs who were baseline ADA-positive and ADA-negative were 17% (17/98) and 9% (1/11), respectively.

When comparing all TEAEs and SAEs as a function of the highest post-treatment ADA titre a significant difference observed between the highest and the lowest titre subgroups. The applicant should clarify whether (i) a local immunogenicity process occurs in the bladder and ADA are able to escape to systemic circulation; or (ii) a fraction of the locally administered dose escapes from the bladder to systemic circulation, which could represent a higher relevant fraction at higher doses, resulting in a systemic immunogenicity process.

Most subjects enrolled in the Phase 1/2, Phase 2 and Phase 3 studies had moderate to strong (score of 2+ or 3+) EpCAM expression. There seemed to be no correlation between the degree of EpCAM expression to treatment response or treatment outcome failure.

EpCAM was highly expressed in essentially all BCG-unresponsive NMIBC patients and there is no correlation between EpCAM staining and VB4-845 efficacy.

Studies on pharmacodynamic interactions with other medicinal products or substances and studies on genetic differences in PD response has not been presented.

Systemic concentrations of VB4-845 were undetectable in nearly all subjects as expected based on dosing directly into the bladder. The Phase 1/2 study demonstrated anti-tumour efficacy of VB4-845 most likely due to local exposure of drug to tumour. This is in stark contrast to the observed safety profile. Please see Clinical safety.

No QT/QTc study was conducted.

There is an apparent dose-dependent clinical response, relating the amount of VB4-845 placed into the bladder (directly and accumulated over treatment) and CR and/or tumour progression. The RP2D and Phase 3 dose selection is endorsed as the higher dose range (≥ 10 mg) reveals higher rates of CR and less tumour progression. Since the dose recommendation has been established at 30 mg and roughly 50% of the patients were included in the group of ≥10 mg, the applicant is encouraged to provide the Clinical Response analysis stratified by the dose levels above 10 mg.

3.3.4. Conclusions on clinical pharmacology

No or minimal systemic exposure of VB4-845 was observed due to dosing directly into the bladder. This is in stark contrast to the observed safety profile. Please see Clinical safety. Several other concerns have to be addressed.

3.3.5. Clinical efficacy

The applicant is seeking a MA for the following ***proposed indications***:

• the treatment and prevention of recurrence of carcinoma in situ (CIS) of the urinary bladder following transurethral resection in BCG-unresponsive patients.

• the prevention of recurrence of high-grade Ta and/or T1 papillary tumours following transurethral resection in BCG-unresponsive patients.

Based on a pivotal, non-randomised, open-label phase 3 study and supportive data from a phase 1/2 and phase 2 study, the applicant is seeking a MA for Oportuzumab.

The applicant sought scientific advice at the CHMP for the first time in 2009 (EMEA/H/SA/1325/1/2009/II). The material provided by the Company for the SA of 2009 indicated that the Company intended to first perform a single arm trial (Trail A) that would be followed by a second confirmatory phase III trial (Trial B) designed as a randomised controlled study. CHMP stated that the Trial A might be useful to gain insight in the magnitude of effect of Oportuzumab. However, the single arm trial (Trial A) was not considered adequate to support conditional/full MA. The CHMP stated in the SA "In conclusion, the Company is advised to proceed to the randomised controlled trial based on the phase II results available and not to divert patients into an uncontrolled trial that is likely to be at most only supportive." The applicant did not follow the advice given from CHMP in 2009 since the pivotal study for the current application is based on the single arm trial. The company requested a

new scientific advice on the clinical development plan on 17 January 2020 (EMEA/H/SA/1325/2/2020/SME/III). The feedback from CHMP was limited since the enrolment of the pivotal study was complete with no possibilities of amending the study. A third SA was requested in Feb 2020 (EMEA/H/SA/1325/3/2020/SME/I) about the chemical, pharmaceutical and biological development.

In study VB4-845-02-IIIA BCG-unresponsive subjects with CIS with and without associated papillary disease and patients with high-grade Ta and/or T1 papillary tumours alone following TURBT, were recruited. This is reflected in the wording of the sought indication which is however not endorsed since:

a) only subjects with urothelial cancer histology were included in the pivotal study.

b) the wording is not reflective of the study design, since evidence for preventing development of disease requires not only lack of disease at baseline but also interpretation of time-dependent endpoints which is not possible in the absence of a comparator. With this in mind it is not possible to isolate the treatment effect of oportuzumab monatox in preventing recurrence of high grade Ta and/or T1 papillary tumours (i.e. the second part of the indication).

c) as mentioned,the pivotal study is a "treatment" study where histologically proven CIS is present in all subjects in cohort 1+2 at baseline, rather than a prophylaxis study where disease would need to have been previously resected. An indication for the prevention of recurrence of CIS is therefore not supported.

Taking all the above into account the wording of the indication should be modified. The following wording is proposed:

"Oportuzumab monatox as monotherapy is indicated for the treatment of Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours in adult patients, following transurethral resection".

Dose-response studies and main clinical studies

Dose selection is based on a phase 1/2 with mainly dose escalation. A dose expansion was conducted from 12 to 18 doses in the induction period and in the maintenance period the dosing schedule was changed from once weekly for three weeks with nine weeks of no drug in the Phase 2 study to every other week in the Phase 3 study for up to 24 months from the start of the induction period to increase overall drug exposure in the pivotal study.

The Phase 1/2 study (VB4-845-02-I) was an open-label, multicentre, dose escalating study of VB4-845 administered to 64 subjects with BCG refractory or intolerant urothelial carcinoma of the bladder, with dose escalation proceeded through 12 doses to a maximum of 30.16 mg and no DLT was observed. Based on the safety, tolerability and preliminary efficacy data from this study (greater overall response rates in the 2 highest dose groups; 1.0 - < 10 mg and ≥10 mg [n=30] and a lower rate of tumour progression in the highest dose group), a 30 mg intravesical dose was chosen for subsequent clinical trials. However, since four dose levels were included within the highest dose group (13.73, 17.85, 23.20 or 30.16 mg), the rationale to choose 30 mg is not clear.

The Phase 2 study (VB4-845-02-IIA) was a single treatment arm, dual-treatment schedule, open label, non-randomised study in 46 subjects with EpCAM-positive, non-invasive urothelial CIS (only 10/45 subjects met the BCG-unresponsive definition) with or without non-invasive papillary disease, who failed or were intolerant to previous treatment with BCG therapy. Two different induction strategies were used in the Phase 2 study. Subjects in Treatment Schedule A (Cohort 1) received an

induction phase of 30 mg once weekly for 6 weeks, followed by 6 weeks of no therapy. Subjects in Cohort 1 who had residual disease (<T2) after induction were permitted to proceed to maintenance or have a second induction course. Subjects in Treatment Schedule B (Cohort 2) received an induction phase consisting of 30 mg once weekly for 12 weeks.

Main study

Study VB4-845-02-IIIA

The Phase 3 study (VB4-845-02-IIIA) is an open-label, non-randomised, multicentre study in subjects with BCG-unresponsive NMIBC (NMIBC in situ (CIS) and/or papillary disease [high grade Ta or any grade T1]). In this study, during the induction phase, subjects received 30 mg of VB4-845 twice a week (BIW) for 6 weeks followed by once weekly for 6 weeks. Although both the Phase 2 and Phase 3 studies used a 30 mg dose of VB4-845, a different dosing regimen was used across the two studies to evaluate the effectiveness to control the disease in subjects with NMIBC. A total of 18 doses were administered with the dosing regimen used in the Phase 3 study as opposed to the 12 doses used in Cohort 2 of the Phase 2 study. Efficacy data in BCG-unresponsive CIS patients has only been generated in the Phase 3 study.

Dose selection:

To increase overall drug exposure in the Phase 3 study without extending the induction period beyond three months, the dosing frequency was increased for the first six weeks, which was also thought to overcome fast growing tumours, where the doubling time has been estimated at 7-10 days. In addition, the maintenance dosing schedule was changed from once weekly for three weeks with nine weeks of no drug in the Phase 2 to every other week for the Phase 3 to more properly reflect the direct killing MOA. The initial (3 month) CR rates for the evaluable subjects in the Phase 3 study and Treatment Schedule B of the Phase 2 study were comparable suggesting both dosing regimens are appropriate.

Cohorts:

The pivotal study was conducted with 3 specified cohorts. Cohorts 1/2 contained subjects with CIS with or without associated papillary disease who recurred before 6 months (86 subjects) and after 6 months but before 11 months (7 subjects) after the last dose of adequate BCG treatment and cohort 3 with subjects with papillary disease but without CIS (40 subjects).

The applicant has chosen to divide the CIS group into two prognostic groups with a shorter and a longer recurrence free period, respectively. This could be interesting in a study with more subjects. With only 7 subjects with a longer recurrence free period it will not be possible to interpret the data. Based on FDA Guidance, an analysis of Cohort 1 + Cohort 2 is considered as the primary efficacy population.

The rationale of not conducting a randomised controlled study is not understood. As there are more than 80,000 new cases of urinary bladder diagnosed every year in the US and NMIBC accounting for approximately 75-85% it is considered feasible to conduct a pivotal study. A controlled study would have provided adequate data to interpret the time to endpoint selected by the applicant (see below). The applicant states that there is no EMA guideline for this situation, however, according to the EMA guideline Points to consider on application with 1. Meta-Analyses; 2. One pivotal study (CPMP/EWP/2330/99): *"In the exceptional event of a submission with only one pivotal study, this has to be particularly compelling with respect to internal and external validity, clinical relevance, statistical significance, data quality, and internal consistency."*

The applicant was advised by the CHMP to subsequently conduct a confirmatory phase 3 trial with a comparator. The rationale for not implementing a randomised controlled trial as originally planned by the applicant (Trial B) is not understood.

For not using a "best available" comparator the applicant argues that since no effective pharmacologic comparator is available for a randomised trial, it will make this trial design unfeasible. They argue that it would be unethical to randomise patients to a comparator arm with limited efficacy, which may lead the disease to progress to a higher stage such as MIBC or metastasis with time. Furthermore, the applicant states that the majority of BCG-unresponsive patients will refuse RC even though there is no non-surgical treatment option available.

The applicant's arguments are challenged. Since the effectiveness of Oportuzumab is not yet established without a randomised trial it is considered ethical to randomise the patients. BCG-unresponsive patients refusing RC could be avoided by enrolling solely patients not eligible for or unwilling to undergo RC.

Title of Study

An Open-Label, Multicentre, Phase 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium™ in Subjects with Non-Muscle-Invasive Carcinoma in Situ (CIS) and/or High-Grade Papillary Disease of the Bladder Previously Treated with Bacillus Calmette-Guérin (BCG).

Methods

Study Participants

Main inclusion criteria

To qualify for participation, each subject must have met all of the following criteria at the baseline visit:

1. Histologically confirmed non-muscle invasive urothelial carcinoma (transitional cell carcinoma) of the bladder as follows:

• CIS (with or without papillary disease) OR

• Any grade T1 papillary disease OR

• High-grade Ta papillary disease

based on a biopsy within 8 weeks of the initial dose of study treatment. If multiple bladder biopsies are required to confirm eligibility, the last bladder biopsy to the initial dose of study treatment must be within 8 weeks. This diagnosis must be confirmed by the independent central pathology reviewer prior to subject enrolment.

A subject with persistent T1 disease on the second (i.e., restaging) TURBT may be enrolled in this study only if the Investigator documents the subject declines cystectomy.

2. Subjects must have received adequate BCG treatment defined as at least 2 courses of BCG, i.e., at least one induction and one maintenance course or at least 2 induction courses. The initial induction course must have been at least 5 treatments within a 7-week period. The second course (induction or maintenance) must have been at least 2 treatments within a 6-week period. The "5+2" doses of BCG must have been given within approximately 1 year (i.e., the start of one course to start of the second course within 12 months ±1 month) and for the same disease episode for which the subject is

enrolling. Treatment must be considered "full-dose" BCG. If additional doses or courses of BCG above the minimum "5+2" were given, these did not have to be within the same approximate 12-month timeframe.

Subjects who were unable to receive at least 5 doses of BCG in a first course and at least 2 doses of BCG in a second course due to intolerance were not eligible.

Subjects who began their initial course of BCG with "full-dose" BCG and required dose-reductions due to adverse events but were still able to tolerate at least "5+2" doses of BCG were considered to meet the requirement for "adequate BCG." Subjects who received less than "full dose" BCG (e.g., 1/3rd dosing) as a standard regimen and not due to dose reductions because of AEs were not eligible.

BCG may have been given in combination with interferon. When BCG was given simultaneously in combination with interferon, 1/3rd dosing of BCG was acceptable.

3. The subject's disease was refractory or had relapsed following adequate BCG treatment. Refractory disease is defined as disease which persists at the first evaluation following adequate BCG. Relapsed disease is defined as having a complete response to adequate BCG but recurs at a subsequent evaluation.

Subjects were enrolled into one of three cohorts based on their type of disease and the time to refractory/relapsed disease following their last dose of BCG as follows:

• Cohort 1: Subjects with CIS with or without associated papillary disease whose disease is determined to be refractory or recurred within 6 months of the last dose of adequate BCG treatment

• Cohort 2: Subjects with CIS with or without associated papillary disease whose disease is determined to have recurred more than 6 months but within 11 months of the last dose of adequate BCG treatment

• Cohort 3: Subjects with high-grade Ta or any grade T1 papillary disease (without CIS) whose disease recurred within 6 months of the last dose of adequate BCG treatment

For eligibility and cohort assignment: 6 months is defined as 30 weeks i.e., 26 weeks (6 months) plus an additional 4 weeks to accommodate scheduling variations and for diagnostic work-up and 11 months is defined as 50 weeks i.e., 48 weeks (11 months) plus an additional 2 weeks to accommodate scheduling variations and for diagnostic work-up.

For subjects enrolling in Cohort 2: The Investigator documents he/she would not treat the subject with additional BCG at the time of study entry.

4. Male or non-pregnant, non-breastfeeding female, age 18 years or older at date of consent.

5. All women of childbearing potential (WOCBP) must have a negative pregnancy test within 7 days of the first dose of study therapy. A woman is not of childbearing potential if she has undergone surgical sterilisation (bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy) or if she is ≥55 years of age and has had no menstrual bleeding of any kind including menstrual period, irregular bleeding, spotting, etc., for at least 12 months and there is no other cause of amenorrhea (e.g., hormonal therapy, prior chemotherapy).

6. All sexually active subjects agreed to use barrier contraception (i.e., condoms) while receiving study treatment and for 120 days following their last dose of study treatment. WOCBP and males whose sexual partners are WOCBP agreed to use barrier contraception and a second form of contraception while receiving study treatment and for 120 days following their last dose of study treatment.

7. Karnofsky performance status ≥ 60 (see study protocol in Appendix 16.1.1).

8. Adequate organ function, as defined by the following criteria:

a. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x upper limit of normal (ULN);

b. Total serum bilirubin ≤1.5 x ULN (CTCAE Grade ≤1);

c. Serum creatinine ≤1.5 x ULN; or a creatinine clearance ≥40 mL/min;

d. Haemoglobin ≥8.0 g/dL;

e. Absolute neutrophil count ≥1500/mm^3;

f. Platelets ≥75,000/mm^3.

9. Ability to understand and sign an Independent Ethics Committee- or Institutional Review Board-approved informed consent document indicating that the subject (or legally acceptable representative) has been informed of all aspects of the trial and is willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures. The informed consent document must be signed prior to the subject undergoing tests or procedures solely for determining study eligibility and prior to receiving any protocol treatment.

Main exclusion criteria

A subject was to be excluded from the study if he/she met any of the following:

1. Evidence of urethral or upper tract TCC by biopsy or upper tract radiological imaging (e.g., intravenous pyelogram, computed tomography urogram, or retrograde pyelogram) within the past 2 years;

2. Subjects with hydronephrosis;

3. Prior intravesical chemotherapy or investigational or anti-cancer treatments within the last 2 months, inclusive of single-dose adjuvant intravesical chemotherapy immediately post-TURBT;

4. Subjects with existing severe urinary tract infection or recurrent severe bacterial cystitis;

5. Subjects with active, uncontrolled impairment of the renal, hepatobiliary, cardiovascular, gastrointestinal, urogenital, neurologic, or hematopoietic systems which, in the opinion of the Investigator, would have predisposed the subject to the development of complications from the administration of intravesical therapy and/or general anesthesia;

6. Subjects who, in the opinion of the Investigator, could not tolerate intravesical administration or intravesical surgical manipulation (cystoscopy, biopsy) due to the presence of concomitant serious illness (e.g., uncontrolled cardiac or respiratory disorders);

7. The subject was pregnant or breast feeding;

8. Women of reproductive age (who were not either medically or surgically incapable of bearing children) and all men could not participate unless agreeing to use double barrier contraception or committing to abstinence during the period of therapy.

The inclusion/exclusion criteria do not clearly define a second line patient population, who had recurrence of CIS, high grade Ta and/or T1 papillary tumours of the urinary bladder following transurethral resection, i.e. BCG-unresponsive despite administration of an appropriate number of BCG doses given and still in a good condition (Karnofsky performance status ≥ 60). The subjects were

allowed though to have received other intravesical therapies (e.g. gemcitabine, epirubicin, mitomycin which are still used in the daily clinic and with some evidence). However, section 4.1. of the SmPC does not reflect the included patient population as argued earlier regarding wording of the indication.Regarding cohort 1 and 3 the subjects must have been determined to be refractory or recurred within 6 months of the last dose of adequate BCG treatment. This is not in line with the scientific advice given by the CHMP in 2009. The CHMP recommended that the subjects should have recurred within the last 12 months. The applicant should clarify.

According to the original protocol as of 3 April 2015 bladder biopsy mapping the location of the tumour(s) and quantifying the affected area of bladder within 8 weeks before study drug administration should be performed. This was retained from the inclusion/exclusion criteria. The applicant should clarify the reason why and if these mappings actually were performed.

Treatments

Subjects received study drug treatments twice weekly (BIW) for 6 weeks and once weekly for 6 weeks during the Induction Phase, and then entered the Maintenance Phase, if eligible:

Study Phase	Treatment Regimen
Induction Phase (Weeks 1-12)	One intravesical dose of Vicineum 30 mg in 50 mL saline instilled twice weekly (BIW) for 6 weeks followed by once weekly for 6 weeks, for a total of 12 weeks. The twice weekly doses are to be administered at least 48 hours apart (and no more than 2 doses may be administered within a calendar week, i.e., within a Sunday through Saturday period). As an example, while a Monday/Thursday or Tuesday/Friday would be optimal, a Monday/Wednesday or a Tuesday/Thursday dosing schedule could be used. There will be a total of 18 doses over the 12-week period of the induction phase.
Maintenance Phase (up to Week 104)	One intravesical dose of Vicineum 30 mg in 50 mL saline instilled once every other week, for up to 24 months (Week 104) from the start of the induction phase.

Oportuzumab solution was thawed at room temperature and then diluted in phosphate buffered saline (PBS) (pH 7.4) up to a total volume of 50 mL. All doses of study drug were administered to the subject at the study site on an outpatient basis. Subjects were advised to refrain from fluid intake 2 hours prior to and during the 2-hour period that study drug was held in the bladder to reduce urine flow during the instillation and dwell of Oportuzumab. Subjects emptied their bladder immediately prior to study drug administration, after which a catheter was inserted. An appropriate local anesthetic and sterile lubricant may have been used at the time of catheterisation. In addition, an oral antibiotic may have been given prophylactically at the time of catheterisation, at the discretion of the Investigator. The subject was requested to move periodically in order to ensure adequate drug distribution within the bladder. At the end of 2 hours, the bladder was emptied by having the subject void.

The dose and schedule of Oportuzumab is somehow unproven in the pivotal study because there has been taken a considerably large dose expansion place compared to the overall drug exposure in the phase 2 study. Furthermore, only a few patients were treated with the 30 mg dose, and the rationale to choose 30 mg is not clear. The applicant should justify and discuss the feasibility of treating the subjects with an unproven dose schedule with no long-term safety data.

Compared to the "full-dose" BCG regimen requiring minimum 7 visits in the hospital with an induction course of 5 treatments the treatment regimen of Oportuzumab requires 18 visits in the induction period followed by up to 46 visits every other week (week 104) in the maintenance period which is indeed not negligible and could cause much inconvenience for the subject with a numerous number of visits followed by interventions in the clinic. The applicant is asked to discuss this.

Objectives

With the presented study, the applicant aims to assess the efficacy and safety of Oportuzumab as monotherapy in subjects with NMIBC CIS with or without papillary disease or high-grade Ta/any grade T1 papillary disease - who failed previous treatment with BCG.

The tolerability of Oportuzumab given for up to 2 years has not been assessed earlier as Oportuzumab in the phase 2 study was only given for up to 51 weeks including long periods without treatment. Please see earlier.

Outcomes/endpoints

Primary Endpoints:

Complete Response (CR) Rate:

The primary endpoints of CR and DoR do only apply to subjects with CIS and not for the subjects in cohort 3. For the subjects in cohort 3 there has not been formulated any primary endpoints.

The applicant has changed the primary endpoint while the study was ongoing (see section Changes to the protocol). In the CSR, the applicant has chosen to evaluate the CR at 3 months as primary outcome. The choice of CR at Month 3 as primary endpoint has several drawbacks. The timepoint is considered not sufficient to evaluate response since the induction period is 6 months. A confirmatory CR at 6 months has therefore a higher clinical relevance for efficacy evaluation. It is acknowledged that assessment of efficacy at 3 months is needed to offer the subject the possibility of surgery in case of progression. CR at 6 months is also in line with what CHMP has commented in the scientific advice given back in 2009. Response rates are accepted endpoints for demonstration of activity in single arm trials. However, the CR at 6 and 12 months have been calculated and the endpoint of CR at 6 months can be considered and assessed as such.

According to the criteria for treatment failure it seems that the 2004 WHO grading system has been used, but in this case not all Ta G2 lesions can be considered low-grade carcinoma, as suggested. The definition of low-grade disease that is considered a complete response should be clarified.

Duration of Response (DoR):

DoR is not considered an adequate primary endpoint in this setting since time-dependent endpoints are highly sensitive to prognostic factors and not only to tumoural response. The clinical interpretation of the DoR is difficult due to the lack of comparator arm in an open label study, and the fact that this endpoint is based on a post-study initiation variable. According to the EMA Guideline on the clinical evaluation of anticancer medicinal products (EMA/CHMP/205/95 Rev.6) *"Response duration comparing groups of patients on different therapies may be regarded as informative. Data should be reported with confidence intervals for the individual study arms, but significance testing comparing duration of response between study arms should not be undertaken as the comparison refers to groups that are not fully randomised. "Time in response" where patients without response are assigned a duration of zero enables a statistical comparison between study groups."* Additional sensitivity analyses were requested in the statistical section.

Secondary Endpoints:

Complete Response Rate at 6,9, and 12 months in subject with CIS.

Sustained Complete Response (sCR) Subjects who have CR at the primary assessment will have a sustained CR if at the time of any disease status evaluation (per protocol every 13 weeks or any unscheduled evaluation) there is no evidence of CIS, high-grade Ta or any grade T1 disease or disease progression.

• Time to disease recurrence: defined as the time from the date of first dose of study treatment to treatment failure or disease progression (e.g., T2 or more advanced disease).

• Time to cystectomy: defined as the time from the date of first dose of study treatment to surgical bladder removal.

• Event-free survival (EFS): defined as the time from the date of first dose of study treatment to the first point of treatment failure or death as first event.

• Progression-free survival (PFS): defined as the time from the date of first dose of study treatment to disease progression (e.g., T2 or more advanced disease) or death as a first event.

• Overall survival (OS): defined as the time from the date of first dose of study treatment to death from any cause.

The secondary endpoint of complete response rate is considered clinically relevant. The other secondary endpoints are all time-dependent and, as mentioned earlier, lack clinical interpretation in the context of a study without a comparator. Time-to-recurrence demands a follow-up time of the subjects of at least 2 years for CIS and 3 years for high-grade papillary disease as recommended by CHMP in 2009. This is crucial for the documentation of disease progression after recurrence of disease and after Oportuzumab is discontinued. The applicant is requested to clarify if this was planned in the follow-up and if yes how the follow-up was conducted (ex. outpatient or by phone). Further, minimum and median time to follow-up of all patients from Cohort 1+2 and Cohort 3 that discontinued treatment should be provided..

To summarize, the primary endpoint CR at 3 months is not considered informative and the CR at 6 months is preferred. The choice of DoR as primary endpoint is not endorsed. The secondary endpoint CR at different timepoints is considered clinically relevant. The other endpoints are time to event endpoints and therefore the interpretation of the results is hampered by the lack of comparator.

Randomisation and blinding (masking)

This was a non-randomised, open label single-arm study.

According to the SAP v. 2 (page 25/43), the DSMB reviewed limited efficacy data while the study was ongoing. The applicant is requested to explain which efficacy data was reviewed by the DSMB, the rationale of such review and which results were communicated to the Sponsor including timelines. Documentation should be provided.

Statistical methods

Sample size:

Assuming the true complete response rate at 12 months is 30%, sample sizes associated with various widths of two-sided, exact (Clopper-Pearson) 95% confidence intervals are provided as follows:

Sample Size (N)	Target Distance from P to Lower	Proportion (P)	Lower Limit
121	0.080	0.300	0.220
95	0.090	0.300	0.210
76	0.100	0.300	0.200

Under the provided assumptions, a sample size of ≥ 77 evaluable subjects with early relapsed/refractory CIS with or without papillary disease was sufficient to estimate complete response rate with an exact 95% confidence interval that excludes 0.2.

It is noted that the primary endpoint was changed during the course of the study (see Section Changes to the protocol). According to the sample size, a minimum of 77 evaluable subjects would be needed to exclude a CR rate at 12 months of 20%. This is applicable to the first version of the protocol. However, the primary endpoint was changed but the sample size calculations were not revised. It is not understood why the CR at 12 months was used for the sample size calculations when the primary endpoint was CR at 3 months. Thus, the power of the study for the primary endpoint is unknown. Assuming that the number of responders at 3 months is higher than at 12 months, the study is expected to be powered to exclude a lower bound of the 95% CI of CR at 3 months of 20%.

It is also unclear why the study was powered for a secondary endpoint which was not controlled for multiplicity. The sample size calculation does not seem taken into account study discontinuation, initiation of another therapy before progression, or RC. In conclusion, the presented sample size is not relevant to the current study.

Analysis population:

All enrolled population includes subjects who signed an informed consent form and were registered into the central enrolment system.

The modified intent-to-treat (mITT) population is comprised of all subjects who received at least one dose of study medication. This was considered the primary population for efficacy.

The evaluable population includes any subject in the mITT population who completes the induction phase. This population is used for secondary analyses of the efficacy endpoints.

The mITT population, defined as all included subjects who received at least one dose of study drug was used for the primary analysis. This is not endorsed since it would be of concern that a subject recruited to a single arm trial does not receive study drug. In the study, the ITT and the m-ITT are identical and therefore supplementary analysis using the ITT are not requested.

Primary endpoint: CR at Month 3

The primary outcome measure is the complete response rate in subjects with refractory /relapsed CIS or CIS plus papillary disease (i.e., cohorts 1 and 2) following the initiation of Oportuzumab therapy. Ninety-five percent (95%) confidence intervals around the complete response rate at each assessment will be calculated using the Clopper-Pearson method.

Patients who discontinue or die before Month 3 will be included in the denominator of the primary analysis.

Sensitivity analysis

Sensitivity analysis will be conducted where subjects who have a missing centrally read pathology and/or centrally read cytology at a visit where there was an abnormal cystoscopy will be imputed as a

treatment failure for that visit if the subsequent visit indicates treatment failure. A second sensitivity analysis will be performed where subjects with low grade Ta are treated as a failure.

. According to the SAP (page 28/43) sensitivity analyses for CR at Month 3 and DoR for subjects with missing pathology data and missing visits were planned. Those analysis could not be found in the CSR. The applicant is requested to indicate where the planned sensitivity analyses for CR and DoR could be found or to present them, if they were not included in the Dossier.

A sensitivity analysis considering low grade Ta as failure has been provided and results are consistent with the primary analysis. An additional sensitivity analysis considering also low grade T1 as failure (in addition to low-grade Ta) should be provided.

Primary endpoint: Duration of response

Duration of response will be estimated (Kaplan-Meier Estimate) for those subjects who experience a complete response. Subjects who do not experience treatment failure or death will be censored at the time of the last non-missing response assessment.

Sensitivity analysis

Sensitivity analysis will be conducted where subjects who have a missing centrally read pathology and/or centrally read cytology at a visit where there was an abnormal cystoscopy will be imputed as a treatment failure for that visit if the subsequent visit indicates treatment failure. A second sensitivity analysis will be performed where subjects with low grade Ta are treated as a failure.

DoR was calculated using the Kaplan-Meier method, which is agreed. The censoring rules are not understood. It seems that patients who were lost to follow-up were censored.

The applicant is requested to clarify the censoring rules implemented for DoR.

In addition, the applicant should present a sensitivity analysis for DoR where patients lost to follow-up, or who discontinued the study drug before progression, or who died before documented progression are considered events. Only patients ongoing in the study with study drug should be censored if they not experienced progression. If the applicant has information about progression beyond study drug discontinuation, a sensitivity analysis based on observed data regardless of study treatment adherence should also be presented.

The applicant is requested to present an analysis on Time in Response, as indicated in the EMA Guideline on the clinical evaluation of anticancer medicinal products EMA/CHMP/205/95 Rev.6 (Section 7.6.5). In this analysis, all patients in the ITT are included. Patients who did not experience response are included with time zero and patients who experienced response are included with the observed time in response. Patients who discontinued the study or the study drug should be considered events. Kaplan-Meier estimates and a time-to-event curve should be presented.

Secondary endpoint: EFS

Median EFS was estimated using the Kaplan-Meier method. Protocol-defined events in the analysis of event-free survival are:

• Treatment failure. Subjects with a treatment failure at their Post-Induction Phase assessment were considered to have a treatment failure at the time of assessment.

• Death (as a first event)

Table 11: Censoring scheme for EFS

Situation	Date of Event or Censoring	Outcome
Treatment failure	Date of treatment failure	Event
Death without treatment failure and occurring prior to treatment discontinuation	Date of death	Event
Death without treatment failure and occurring after treatment discontinuation	Date of last evaluable disease assessment on or prior to treatment discontinuation[a]	Censored[a]
No baseline disease assessment	Date of first dose	Censored
No on-study disease assessments and no death	Date of first dose	Censored
No treatment failure and no death	Date of last evaluable disease assessment	Censored
New anti-cancer therapy received without treatment failure and reported prior to or on the same day as disease assessment	Date of last evaluable disease assessment on or prior to the date of initiation of subsequent therapy	Censored
Second non-NMIBC cancer reported prior to or on the same day as disease assessment	Date of last evaluable disease assessment on or prior to the date of diagnosis of non-NMIBC cancer	Censored
a This censoring rule acknowledges that disease assessments were not recorded after treatment discontinuation due to an AE.		

Source: SAP v2 page 19/43.

Subjects without evidence of a treatment failure who are diagnosed with upper or lower urinary tract urothelial carcinoma by histology, cytology or radiographic evidence were censored at the date of diagnosis. Subjects without evidence of a treatment failure who undergo cystectomy were censored at the date of cystectomy. All other subjects were censored at the time of last assessment including long term follow-up (LTFU).

EFS was calculated using the Kaplan-Meier method, which is agreed.

The censoring rules are not fully understood. The applicant is asked to clarify why subjects without evidence of a treatment failure who are diagnosed with upper or lower urinary tract urothelial carcinoma by histology, cytology or radiographic evidence were censored at the date of diagnosis.

The applicant should present a sensitivity analysis for EFS where patients lost to follow-up, or who discontinued the study drug before treatment failure or death are considered events. Only patients ongoing in the study with study drug should be censored if they not experienced an EFS event. If the applicant has information about progression and death beyond study drug discontinuation, a sensitivity analysis based on observed data regardless of study treatment adherence should also be presented.

Multiplicity considerations

No multiple comparison adjustments were performed (see earlier MO).

Changes to the SAP and to the planned analyses

Based on FDA Guidance, an analysis of Cohort 1 + Cohort 2 is now planned as the primary efficacy population. In particular, the FDA has stated that recurrence of bladder cancer within 12 months of

BCG is an acceptable study population for investigational agents in this setting. This change is documented throughout the SAP.

The SAP was revised on October 27, 2020 to generate datasets including tables, listings and figures for the 24-month follow up analysis.

Date	Revision	Rationale
27OCT2020	Updated Section 3.3.8 by study visit windows for maintenance month and long-term follow-up windows	Updated for 3 months to cover 91 days (i.e. 13 weeks) instead of 12 weeks for consistency with response assessments which occur every 13 weeks during maintenance.
27OCT2020	Removed third sensitivity analysis for efficacy endpoints	Data collection did not allow for determination of upper and lower tract disease.

Source: SAP page 31/4

There are two versions of the SAP. The first version was dated 18 September 2019 and the second version was dated 27 October 2020. The data cut-off date is 6 October 2020.

The applicant should provide a word document with track changes from version 1 to version 2 of the SAP.

It is noted that the time window for the efficacy analysis was modified in version 2 of the SAP (one week was added). The applicant is requested to present the analysis for CR at 3, 6,9, 12, 18 and 44 months, sCR at different time points and DoR using the original time window.

Regarding changes to the planned analysis, the primary analysis population was changed to include only cohort 1 and 2 based on an FDA recommendation.

Of note, the applicant present the CSR as "Interim Report 2". The applicant is asked to list and clarify which changes were made from the first version, which should also be provided.

The design and conduct of the pivotal study are not considered adequate for a pivotal study:

a) The expected effect size or efficacy hypothesis of the study was not mentioned in the protocol. Nor was the response criterium required to consider the study successful described. According to the original sample size calculation, the CR obtained at 12 months was expected to be larger than 20%. The CR at 12 months observed in the current study is (Cohort 1 + 2) is 15 responders of 93 included participants: 16.1% with 95 % CI (9.3%; 25.2%) (Assessor's own calculations). The lower bound of the confidence interval is indeed lower than 20% in the study. According to the applicant's sample size calculations sufficiently statistical power was obtained with 77 subjects. Therefore, the study is clearly powered to show whether CR at month 12 is higher than 20%. The applicant is requested to clarify why the study is considered successful.

b) The primary endpoint was changed 3 times during the course of the study and the wording differs between the protocol amendment 3 and the CSR. In particular, in the protocol CR at 6 months is implemented with CR at 3 months was reported in the CSR. The applicant is asked to clarify why the primary endpoint was changed while the study was ongoing and the use of CR at 3 month as primary endpoint;

c) The study is not controlled for multiplicity for neither primary nor secondary endpoints. The applicant is requested to justify this approach in a pivotal study.

Results

Participant flow

There were 204 subjects screened with 133 subjects enrolled consisting of 93 subjects with CIS with or without papillary disease and 40 subjects with papillary disease. Overall 110/133 subjects (83%) did not complete the entire course of the study. Primary reason for early termination was treatment failure in 96/133 subjects (72%) and AE in 4/133 (3%).

To exclude that observed effects are the result of a favourable selection of the study population, details about the screening process (particularly the extent to which all potentially eligible patients within a centre were screened), the decision for trial inclusion, and about subjects not selected should be provided by the applicant.

Table 12: Subjects termination from study (mITT population)

	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=86)	Cohort 2: CIS With or Without Papillary Disease Within 6 – 11 mo of BCG (N=7)	Cohort 1 + Cohort 2: All CIS With or Without Papillary Disease (N=93)	Cohort 3: Papillary Disease (N=40)	Overall (N=133)
Did the subject complete the entire course of the study?*					
No	76 (88%)	6 (86%)	82 (88%)	28 (70%)	110 (83%)
Yes	10 (12%)	1 (14%)	11 (12%)	12 (30%)	23 (17%)
Primary reason for early termination					
Withdrawal of informed consent	0	0	0	2 (5%)	2 (2%)
Pregnancy	0	0	0	0	0
Treatment failure	70 (81%)	5 (71%)	75 (81%)	21 (53%)	96 (72%)
Adverse event	2 (2%)	0	2 (2%)	2 (5%)	4 (3%)
Persistent non-compliance	0	0	0	0	0
Investigator decision	0	0	0	2 (5%)	2 (2%)
Intercurrent illness	0	0	0	0	0
Sponsor decision	1 (1%)	0	1 (1%)	0	1 (< 1%)
Lost to follow-up	0	0	0	1 (3%)	1 (< 1%)
Protocol violation	1 (1%)	0	1 (1%)	0	1 (< 1%)
Other	2 (2%)	1 (14%)	3 (3%)	0	3 (2%)

Abbreviations: BCG=Bacillus Calmette-Guérin; CIS=carcinoma in situ; mITT=modified intent-to-treat

Additional information: Days on study drug is defined as the date of last dose of Vicineum – date of first dose of Vicineum +1.

Days on study is defined as the number of days from initiation of study drug to date off study as noted on the CRF. For subjects who are ongoing, Days on study is defined as the number of days from initiation of study drug to the last visit.

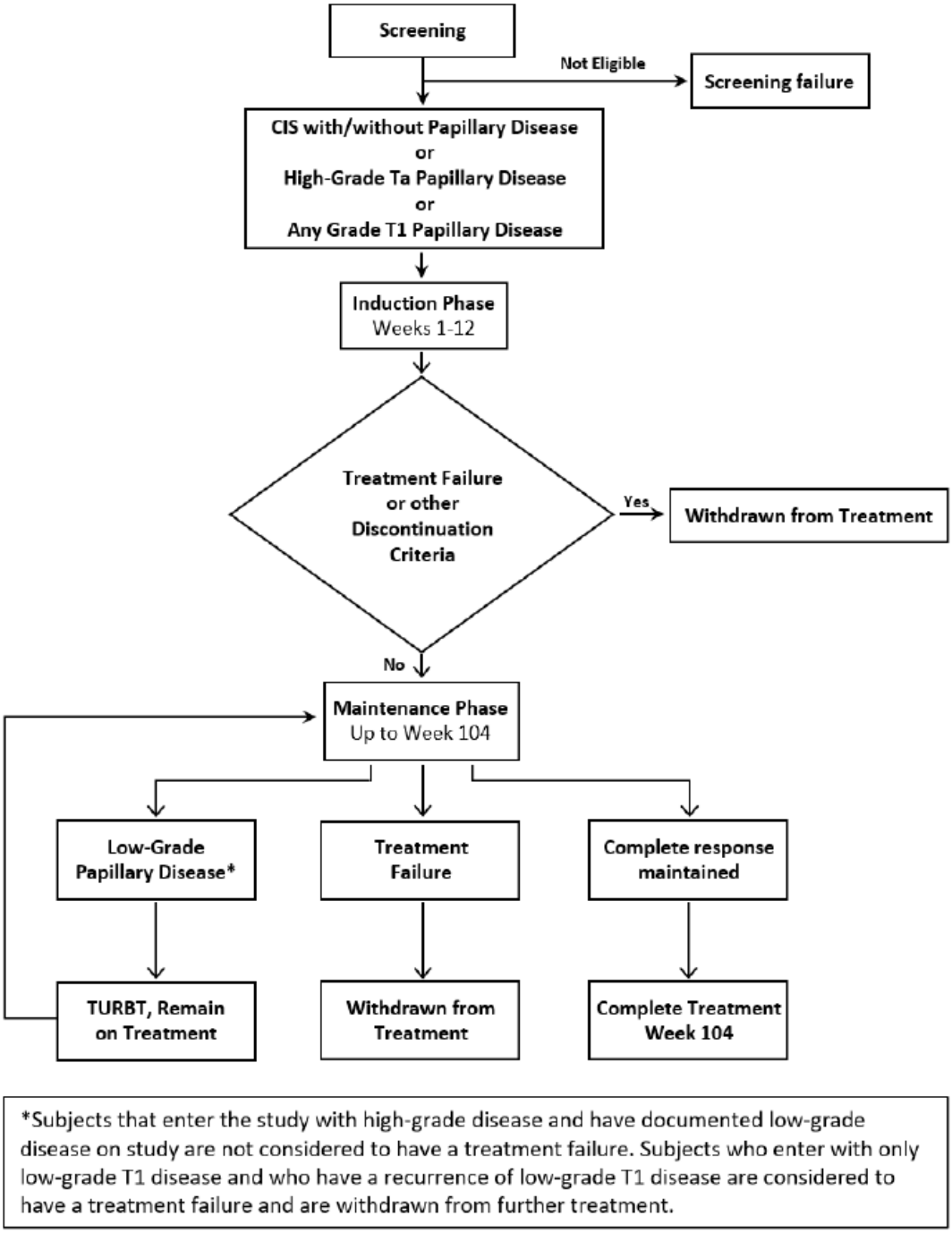
*Course of study is 2 years and includes induction (3 months) and maintenance (21 months).

Data source: Table 14.1.2

There were 6 subjects excluded from the evaluable patient population: one subject each for withdrawal of informed consent, lost to follow-up, protocol violation, patient was determined by the Sponsor to have been ineligible for enrolment, Investigator decision and two subjects due to adverse events.

A comprehensive description of the progress of the study participants through the trial, including the number of patients that completed the induction phase and entered the maintenance phase, should be

provided. The applicant has provided a diagram as below but should fill out the table above to give an overview of the flow of the progress of study participants through all the phases of the trial:



Overall 110/133 subjects (83%) did not complete the entire course of the study. Primary reason for early termination was treatment failure in 96/133 subjects (72%) and AE in 4/133 (3%).

Recruitment

Study initiation date: 29 September 2015

Study completion date: 08 May 2020

The clinical trials were conducted in the United States and Canada with 75 sites participating. Although the studies were all conducted outside of the European Union, the patient population and treatment approaches for NMIBC are considered analogous to that in Europe.

Conduct of the study

The protocol as of 3 April 2015 was amended three times. Changes in the first amendment were conducted before the first patient was enrolled in the study. The second amendment as of 22 June 2016 included the definition of adequate BCG treatment and the requirement for additional clinical chemistry testing during the induction and maintenance phase.

The applicant should clarify if the subjects enrolled in the study until June 2016 have had sufficient BCG treatment before treated with Oportuzumab and how many subjects were enrolled before this date. Information on the number of patients by Cohort who were BCG refractory and those who were relapsed should be provided.

The applicant is requested to provide a sensitivity analysis where subjects not treated with sufficient BCG are withdrawn from the efficacy analyses.

The third amendment as of 26 January 2017 included that chemistry lab must be drawn each week with 1 day before the 2nd dose of that week, and the results must be reviewed prior to the administration of the 2nd Oportuzumab dose of that week. The applicant should clarify and elaborate on if lacking chemistry lab could cause a safety risk for the subjects enrolled and treated before January 2017 and how many subjects were treated without sufficient chemistry lab.

The applicant has provided a listing of significant protocol deviations by subject. According to the applicant there was only one protocol deviation resulting in withdrawal from the study. However, in order to facilitate the assessment the applicant should provide an overview table of the type of protocol deviations/major violations including how many subjects affected and the applicant should justify the removal of a subject from the study.

Regarding changing of the primary endpoint during the three amendments and during the course of the study together with the use of CR at 3 months as primary endpoint, please see earlier MO.

Baseline data

	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=86)	Cohort 2: CIS With or Without Papillary Disease Within 6-11 months of BCG (N=7)	Cohort 1 + Cohort 2: Total CIS With or Without Papillary Disease (N=93)	Cohort 3: Papillary Disease (N=40)	Overall (N=133)
Age at Informed Consent (years)					
N	86	7	93	40	133
Mean (SD)	73.7 (8.54)	68.3 (9.35)	73.3 (8.67)	74.0 (9.14)	73.5 (8.79)

Median	73.4	67.0	73.1	74.6	73.6
Min, Max	55.3, 91.9	56.7, 84.8	55.3, 91.9	54.3, 92.9	54.3, 92.9
Gender					
Male	63 (73%)	6 (86%)	69 (74%)	34 (85%)	103 (77%)
Female	23 (27%)	1 (14%)	24 (26%)	6 (15%)	30 (23%)
Race					
American Indian or Alaska Native	0	0	0	0	0
Asian	2 (2%)	0	2 (2%)	1 (3%)	3 (2%)
Black or African American	4 (5%)	0	4 (4%)	1 (3%)	5 (4%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	79 (92%)	7 (100%)	86 (92%)	38 (95%)	124 (93%)
Other[1]	1 (1%)	0	1 (1%)	0	1 (< 1%)
Ethnicity					
Hispanic or Latino	1 (1%)	1 (14%)	2 (2%)	1 (3%)	3 (2%)
Not Hispanic or Latino	85 (99%)	6 (86%)	91 (98%)	35 (88%)	126 (95%)
Not Reported	0	0	0	0	0
Unknown	0	0	0	4 (10%)	4 (3%)

Abbreviations: BCG=Bacillus Calmette-Guérin; CIS=carcinoma in situ; Max=maximum; Min=minimum; mITT=modified intent-to-treat; SD=standard deviation

[1]Subjects who identified multiple races are categorized as "Other".

Data source: Table 14.1.3

	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=86)	Cohort 2: CIS With or Without Papillary Disease Within 6-11 months of BCG (N=7)	Cohort 1 + Cohort 2: Total CIS With or Without Papillary Disease (N=93)	Cohort 3: Papillary Disease (N=40)	Overall (N=133)
Diagnosis at Last Recurrence[1]					
Tis (CIS)	71 (83%)	7 (100%)	78 (84%)	8 (20%)	86 (65%)
Ta	4 (5%)	0	4 (4%)	21 (53%)	25 (19%)
T1	11 (13%)	0	11 (12%)	10 (25%)	21 (16%)
T2	0	0	0	0	0
Missing	0	0	0	1 (3%)	1 (< 1%)
Disease Stage at Initial Diagnosis[1]					
Tis (CIS)	28 (33%)	2 (29%)	30 (32%)	3 (8%)	33 (25%)
Ta	25 (29%)	3 (43%)	28 (30%)	24 (60%)	52 (39%)
T1	31 (36%)	2 (29%)	33 (35%)	13 (33%)	46 (35%)
T2	2 (2%)	0	2 (2%)	0	2 (2%)
Histological Grade at Initial Diagnosis					
Unknown	6 (7%)	0	6 (6%)	0	6 (5%)
Low	18 (21%)	1 (14%)	19 (20%)	10 (25%)	29 (22%)
High	61 (71%)	6 (86%)	67 (72%)	30 (75%)	97 (73%)
Missing	1 (1%)	0	1 (1%)	0	1 (< 1%)
Months Since Date of Initial Diagnosis[2]					
N	79	7	86	40	126
Mean (SD)	35 (36.7)	60 (42.9)	37 (37.5)	39 (43.3)	38 (39.3)
Median	20	41	22	21	22

Data source: Table 14.1.4

	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=86)	Cohort 2: CIS With or Without Papillary Disease Within 6-11 months of BCG (N=7)	Cohort 1 + Cohort 2: Total CIS With or Without Papillary Disease (N=93)	Cohort 3: Papillary Disease (N=40)	Overall (N=133)
Number of Prior Chemotherapy Treatment Cycles[1]					
N	71	6	77	29	106
Mean (SD)	1 (3.3)	1 (2.3)	1 (3.3)	1 (3.6)	1 (3.3)
Median	0	1	0	0	0
Min, Max	0, 23	0, 6	0, 23	0, 18	0, 23
Last Response to Prior Chemotherapy					
Complete	3 (3%)	1 (14%)	4 (4%)	4 (10%)	8 (6%)
Partial	1 (1%)	1 (14%)	2 (2%)	1 (3%)	3 (2%)
Failed to Respond	13 (15%)	1 (14%)	14 (15%)	3 (8%)	17 (13%)
Missing	69 (80%)	4 (57%)	73 (78%)	32 (80%)	105 (79%)
Number of Prior Radiotherapy Treatment Cycles[1]					
N	71	6	77	29	106
Mean (SD)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.6)
Median	0	0	0	0	0
Min, Max	0, 0	0, 0	0, 0	0, 0	0, 0
Last Response to Prior Radiotherapy					
Complete	0	0	0	0	0
Partial	0	0	0	0	0
Failed to Respond	0	0	0	0	0
Missing	86 (100%)	7 (100%)	93 (100%)	40 (100%)	133 (100%)
Number of Prior BCG Treatment Cycles[1]					
N	86	7	93	40	133
Mean (SD)	3 (2.3)	4 (1.9)	3 (2.2)	3 (2.7)	3 (2.4)
Median	3	3	3	2	3
Min, Max	2, 13	2, 7	2, 13	2, 15	2, 15

The subjects were predominantly male with a male/female distribution of 4:1 as seen in clinical practice. Most of the subjects were white (92%).

"Diagnosis at last recurrence" is considered the histological diagnosis before enrolment in the study and is distributed in cohort 1/2 with CIS (84%), Ta (4%) and T1 (12%). The distribution in cohort 3 (papillary disease only) is distributed with CIS (20%), Ta (53%), T1 (25%) and 1 missing. The applicant is asked to clarify why only 78/93 subjects have CIS when all 93 subjects are expected to have CIS and why 20% in cohort 3 had CIS where no subjects are expected to have CIS.

Tabulated numbers of prior treatment cycles of chemotherapy and radiotherapy for all cohorts with last response to chemotherapy have been provided. The last response to radiotherapy is mentioned as missing but should be mentioned as not evaluable (NE). The number of prior chemotherapy treatment cycles and prior radiotherapy treatment cycles are equal. This is not understood. The applicant should elaborate more thoroughly on the baseline characteristics e.g. how many subjects had prior treatment and which type of chemotherapy was given.

The time allowed between prior intravesical or other chemotherapy treatment and any investigational agent to the initial dose of study drug should be clarified. There are discrepancies between the protocol and the CSR (2 weeks according to the CSR while 2 weeks for prior intravesical or chemotherapy and 4 weeks for any other investigational agent in the Protocol).

The applicant is requested to provide information on the cystoscopy modality (i.e. fluorescence cystoscopy or white-light cystoscopy) used in each responder patient throughout the study (in each visit).

A detailed justification for the changes in the primary efficacy population performed throughout the study should be provided.

The applicant is requested to provide baseline disease characteristics according to the independent central pathology reviewer as compared with the investigator.

Patients included in study VB4-845-02-IIIA had a median of 3 (range: 0, 28) prior TURBT. However, according to these data, it seems that some patients did not receive a TURBT. The applicant should confirm whether prior TURBT was required for all patients before first dose of oportuzumab monatox and provide information of those patients that did not receive a prior TURBT. In addition, the applicant should confirm whether residual disease was present in all CIS patients after TURBT.

Further information on treatment failures (i.e. high-grade disease, progression to metastatic/muscle invasive disease, death) should be provided at each time of assessment for CIS patients.

Numbers analysed

133 subjects were enrolled in the pivotal phase III study with 86, 7 and 40 subjects in cohort 1, 2 and 3, respectively. This was the mITT group. The evaluable group consisted of 127 subjects with 82, 7 and 38 subjects in cohort 1, 2 and 3, respectively.

Table 13. Distribution by analysis population

Populations	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=86)		Cohort 2: CIS With or Without Papillary Disease Within 6 – 11 mo of BCG (N=7)		Cohort 1 + Cohort 2: All CIS With or Without Papillary Disease (N=93)		Cohort 3: Papillary Disease (N=40)		Overall (N=133)	
	N	%	N	%	N	%	N	%	N	%
All Enrolled Population	86	100%	7	100%	93	100%	40	100%	133	100%
Modified Intent to Treat Population	86	100%	7	100%	93	100%	40	100%	133	100%
Primary Efficacy Population	86	100%	7	100%	93	100%	N/A	N/A	93	70%
Evaluable Population	82	95%	7	100%	89	96%	38	95%	127	95%
Induction Phase Dosing Compliant Population	81	94%	6	86%	87	94%	36	90%	123	92%
Study Dosing Compliant Population	85	99%	6	86%	91	98%	38	95%	129	97%

There were 6 subjects excluded from the evaluable patient population: one subject each for withdrawal of informed consent, lost to follow-up, protocol violation, subject was determined by the Sponsor to have been ineligible for enrolment, Investigator decision and two subjects due to adverse events.

The applicant should provide narratives for the 6 subjects excluded from the evaluable population.

Outcomes and estimation

Primary efficacy analysis

CR at 3 months (primary endpoint) and sustained CR (sCR, secondary endpoint):

Table 14.2.1.1.2
Summary of Complete Response by Initial Disease Group and Visit
Primary Efficacy Population

	CIS Alone (N=63)	CIS + Ta (N=14)	CIS + T1 (N=16)	All CIS (N=93)
Number (%) of Subjects with Complete Response at:				
Post Induction Phase	23/ 63 (37%)	6/ 14 (43%)	7/ 16 (44%)	36/ 93 (39%)
95% Confidence Interval [1]	(25%, 50%)	(18%, 71%)	(20%, 70%)	(29%, 49%)
Maintenance Phase				
Maintenance Mth 3	17/ 63 (27%)	6/ 14 (43%)	3/ 16 (19%)	26/ 93 (28%)
95% Confidence Interval [1]	(17%, 40%)	(18%, 71%)	(4%, 46%)	(19%, 38%)
Maintenance Mth 6	12/ 63 (19%)	5/ 14 (36%)	2/ 16 (13%)	19/ 93 (20%)
95% Confidence Interval [1]	(10%, 31%)	(13%, 65%)	(2%, 38%)	(13%, 30%)
Maintenance Mth 9	10/ 63 (16%)	3/ 14 (21%)	2/ 16 (13%)	15/ 93 (16%)
95% Confidence Interval [1]	(8%, 27%)	(5%, 51%)	(2%, 38%)	(9%, 25%)
Maintenance Mth 12	8/ 63 (13%)	3/ 14 (21%)	2/ 16 (13%)	13/ 93 (14%)
95% Confidence Interval [1]	(6%, 23%)	(5%, 51%)	(2%, 38%)	(8%, 23%)
Maintenance Mth 15	8/ 63 (13%)	3/ 14 (21%)	2/ 16 (13%)	13/ 93 (14%)
95% Confidence Interval [1]	(6%, 23%)	(5%, 51%)	(2%, 38%)	(8%, 23%)

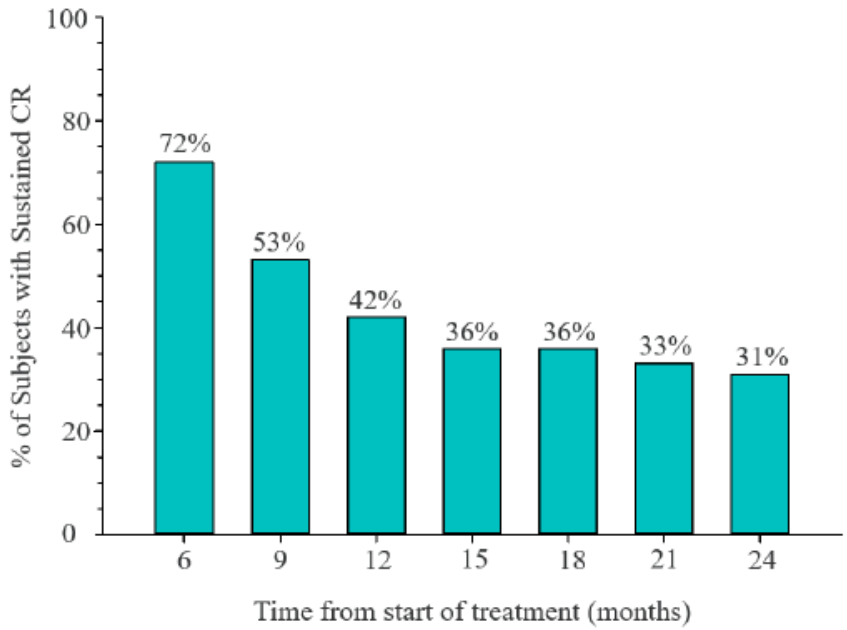
Table 14.2.1.4
Summary of Complete Response by Visit
Evaluable Population: Cohorts 1 and 2

	CIS With or Without Papillary Disease Within 6 mo of BCG (N=82)	CIS With or Without Papillary Disease Within 6 - 11 mo of BCG (N=7)	Total CIS With or Without Papillary Disease (N=89)
Number (%) of Subjects with Complete Response at:			
Post Induction Phase	32/ 82 (39%)	4/ 7 (57%)	36/ 89 (40%)
95% Confidence Interval [1]	(28%, 50%)	(18%, 90%)	(30%, 51%)
Maintenance Phase			
Maintenance Mth 3	22/ 82 (27%)	4/ 7 (57%)	26/ 89 (29%)
95% Confidence Interval [1]	(18%, 38%)	(18%, 90%)	(20%, 40%)
Maintenance Mth 6	16/ 82 (20%)	3/ 7 (43%)	19/ 89 (21%)
95% Confidence Interval [1]	(12%, 30%)	(10%, 82%)	(13%, 31%)
Maintenance Mth 9	14/ 82 (17%)	1/ 7 (14%)	15/ 89 (17%)
95% Confidence Interval [1]	(10%, 27%)	(0%, 58%)	(10%, 26%)
Maintenance Mth 12	12/ 82 (15%)	1/ 7 (14%)	13/ 89 (15%)
95% Confidence Interval [1]	(8%, 24%)	(0%, 58%)	(8%, 24%)
Maintenance Mth 15	12/ 82 (15%)	1/ 7 (14%)	13/ 89 (15%)
95% Confidence Interval [1]	(8%, 24%)	(0%, 58%)	(8%, 24%)

Table 14: Sustained Complete Response Rate (sCR) by Cohort

	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=32)	Cohort 2: CIS With or Without Papillary Disease Within 6 – 11 mo of BCG (N=4)	Cohort 1 + Cohort 2: All CIS With or Without Papillary Disease (N=36)
6 Months (95% CI) [1]	69% (22/32) (50%, 84%)	100% (4/4) (40%, 100%)	72% (26/36) (55%, 86%)
9 Months (95% CI) [1]	50% (16/32) (32%, 68%)	75% (3/4) (19%, 99%)	53% (19/36) (35%, 70%)
12 Months (95% CI) [1]	44% (14/32) (26%, 62%)	25% (1/4) (1%, 81%)	42% (15/36) (26%, 59%)
15 Months (95% CI) [1]	38% (12/32) (21%, 56%)	25% (1/4) (1%, 81%)	36% (13/36) (21%, 54%)
18 Months (95% CI) [1]	38% (12/32) (21%, 56%)	25% (1/4) (1%, 81%)	36% (13/36) (21%, 54%)
21 Months (95% CI) [1]	34% (11/32) (19%, 53%)	25% (1/4) (1%, 81%)	33% (12/36) (19%, 51%)
24 Months (95% CI) [1]	31% (10/32) (16%, 50%)	25% (1/4) (1%, 81%)	31% (11/36) (16%, 48%)

Figure 2: Sustained CR in CIS mITT Subjects with CR at 3 months

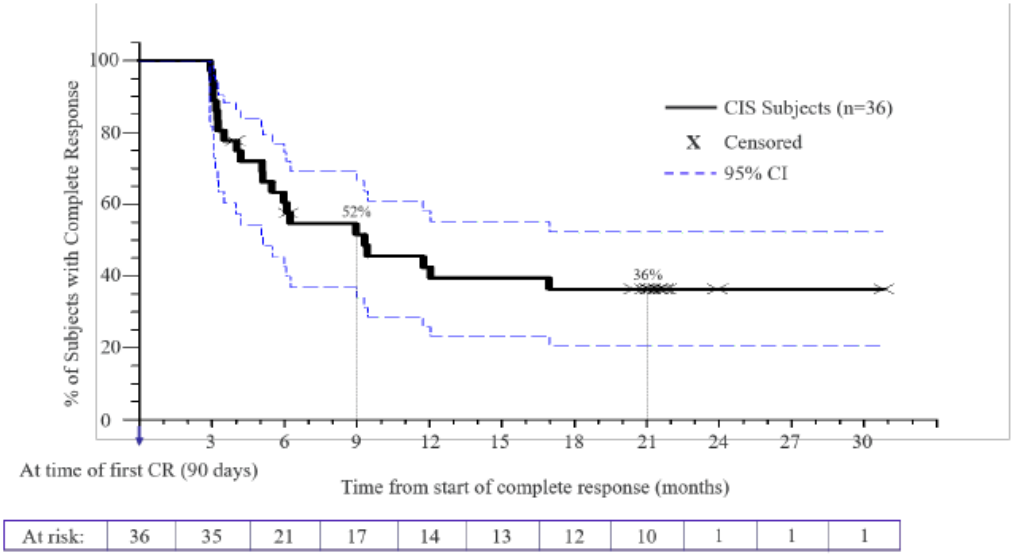


Duration of Response (DoR):

Table 15: Overall Duration of Complete Response: Primary Efficacy Population (All CIS Subjects)

	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=32)	Cohort 2: CIS With or Without Papillary Disease Within 6 – 11 mo of BCG (N=4)	Cohort 1 + Cohort 2: All CIS With or Without Papillary Disease (N=36)
Kaplan-Meier Estimate (days)			
N (Number Censored)	32 (11)	4 (2)	36 (13)
Mean (SE)	455.1 (68.39)	254.0 (35.52)	462.6 (64.51)
Median (95% CI)	273.0 (127.0, 937.0)	283.0 (167.0, NA)	283.0 (155.0, 937.0)
25% - 75%	114.0 – 937.0	225 – NA	122.0 – 937.0

Figure 3: Kaplan-Meier Plot: Duration of Complete Response



The mITT group (CIS) consists of 93 subjects. The CR rate for the mITT subjects at 3 months was 39% (36/93) with 95% CI (29 %; 49%).

The applicant has chosen to evaluate CR at different times using the total number of responders at 3 months in the denominator. All eligible (or all treated with at least one dose) subjects should be included in the denominator for the calculation of the response rate and therefor this trial conclusion should not be based on a selected "evaluable" subset. For patients who were responders at month 3, Table 12 and figure 2 show that the CR was sustained in 72% (26/36), 53% (19/36), 42% (15/36), 36% (13/36), 36% (13/36), 33% (12/36) and 31% (11/36) of those subjects at 6, 9, 12, 15, 18, 21, and 24 months, respectively i.e. at 24 months only 11/89 subjects (12%) had sCR. Given the lack of clinical interpretation of the results in Table 14.2.1.4. this is not considered informative. In addition, sCR has not been controlled for multiplicity neither the study has been powered to this endpoint. In summary, the results for sCR are considered exploratory.

Nevertheless, the CR in the ITT were presented as Complete response rate in Table 16 below. To contextualize CR at 6 months was 28% (26/93), at 12 months 16% (15/93) and at 18 months 14% (13/93). While the sCR seems stable, CR calculated using the m-ITT falls over time to a much larger

extent, indicating that approximately 16% of patients who initiate this therapy will be responders at month 12.

The clinical relevance of the primary endpoint, the short follow-up time and the duration of effect are questioned. The applicant is requested to discuss and justify the following:

a) Recently established complete response benchmarks for new therapies for BCG unresponsive CIS were developed according to AUA/FDA workshop recommendations. A clinically meaningful initial complete response rate (for CIS) or recurrence-free rate (for papillary tumours) of at least 50% at 6 months, 30% at 12 months and 25% at 18 months is recommended. The results of the pivotal study seem not to be in line with these complete response benchmarks. The applicant is requested to discuss the clinical relevance of the primary endpoint. Hence, oportuzumab showed a lack of clinically relevant treatment effect with a poor complete response rate of 16% (CIS) at the originally endpoint of 12 months. A placebo response rate in the current setting is likely. CIS is present at baseline, and sensitivity less than 100% for follow-up cystoscopy with biopsy will fail to find CIS in some patients (e.g. 1 - sensitivity). Accordingly, even if no therapy had been administered, a fraction of patients would be deemed responders (= placebo response rate). Accordingly, unlike ORR, the entire of the CR seen cannot be attributed to drug effect. Please discuss and justify that efficacy has been isolated and thereby scientifically established.

b) Oportuzumab monatox has shown activity in patients with NMIBC with CIS (with or without papillary disease) who are BCG-unresponsive, based on an observed CR rate at 3 months of 39% (36 of 93 patients). However, duration of the effect appears limited, with a median duration of response of approximately 9 months and only 11 patients maintaining the response at 2 years. Whether the observed efficacy results can be expected to translate into clinically meaningful benefit for patients (e.g. a delay in time to cystectomy with no detrimental effect in survival) is uncertain. Further substantiation of the reported data is needed to justify a clinical benefit in the claimed patient population.

c) Retrospective studies show that 24% of CRs developed a NMIBC recurrence after combined-modality therapy (CMT) after mean follow-up of 5.1 years. The median time to first NMIBC recurrence was 19.2 months. Seven (9%) of NMIBC recurrences occurred after 10 years of recurrence-free period. Patients who developed a NMIBC recurrence had similar OS and disease-specific survival (DSS) to those who did not. On multivariate analysis, CIS at the time of MIBC diagnosis was the most important risk factor for NMIBC recurrence [Sanchez A., 2018]. To interpret the data from the pivotal study into clinical meaningfulness demands a longer follow-up than 30 months (see earlier OC). The applicant is requested to discuss the clinically relevance of the primary endpoint and the applicant should discuss and justify the chosen follow-up time together with providing updated data.

<u>Secondary endpoints:</u>

Complete Response Rates:

Table 16: Summary of CR Rates by Visit: Primary and Evaluable Efficacy Populations in Cohort 1, Cohort 2, and Cohort 1 + Cohort 2

Visit Time from Start of Treatment	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG	Cohort 2: CIS With or Without Papillary Disease Within 6 – 11 mo of BCG	Cohort 1 + Cohort 2: All CIS With or Without Papillary Disease
mITT Subjects	**(N=86)**	**(N=7)**	**(N=93)**
3 Months (95% CI)[1]	37% (32/86) (27%, 48%)	57% (4/7) (18%, 90%)	39% (36/93) (29%, 49%)
6 Months (95% CI)[1]	26% (22/86) (17%, 36%)	57% (4/7) (18%, 90%)	28% (26/93) (19%, 38%)
9 Months (95% CI)[1]	19% (16/86) (11%, 28%)	43% (3/7) (10%, 82%)	20% (19/93) (13%, 30%)
12 Months (95% CI)[1]	16% (14/86) (9%, 26%)	14% (1/7) (0%, 58%)	16% (15/93) (9%, 25%)
15 Months (95% CI)[1]	14% (12/86) (7%, 23%)	14% (1/7) (0%, 58%)	14% (13/93) (8%, 23%)
18 Months (95% CI)[1]	14% (12/86) (7%, 23%)	14% (1/7) (0%, 58%)	14% (13/93) (8%, 23%)
21 Months (95% CI)[1]	13% (11/86) (7%, 22%)	14% (1/7) (0%, 58%)	13% (12/93) (7%, 21%)
24 Months (95% CI)[1]	12% (10/86) (6%, 20%)	14% (1/7) (0%, 58%)	12% (11/93) (6%, 20%)

Visit Time from Start of Treatment	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG	Cohort 2: CIS With or Without Papillary Disease Within 6 – 11 mo of BCG	Cohort 1 + Cohort 2: All CIS With or Without Papillary Disease
Evaluable Subjects	**(N=82)**	**(N=7)**	**(N=89)**
3 Months (95% CI)[1]	39% (32/82) (28%, 50%)	57% (4/7) (18%, 90%)	40% (36/89) (30%, 51%)
6 Months (95% CI)[1]	27% (22/82) (18%, 38%)	57% (4/7) (18%, 90%)	29% (26/89) (20%, 40%)
9 Months (95% CI)[1]	20% (16/82) (12%, 30%)	43% (3/7) (10%, 82%)	21% (19/89) (13%, 31%)
12 Months (95% CI)[1]	17% (14/82) (10%, 27%)	14% (1/7) (0%, 58%)	17% (15/89) (10%, 26%)
15 Months (95% CI)[1]	15% (12/82) (8%, 24%)	14% (1/7) (0%, 58%)	15% (13/89) (8%, 24%)
18 Months (95% CI)[1]	15% (12/82) (8%, 24%)	14% (1/7) (0%, 58%)	15% (13/89) (8%, 24%)
21 Months (95% CI)[1]	13% (11/82) (7%, 23%)	14% (1/7) (0%, 58%)	13% (12/89) (7%, 22%)
24 Months (95% CI)[1]	12% (10/82) (6%, 21%)	14% (1/7) (0%, 58%)	12% (11/89) (6%, 21%)

Table 17: Summary of Complete Response by Initial Disease Group and Month

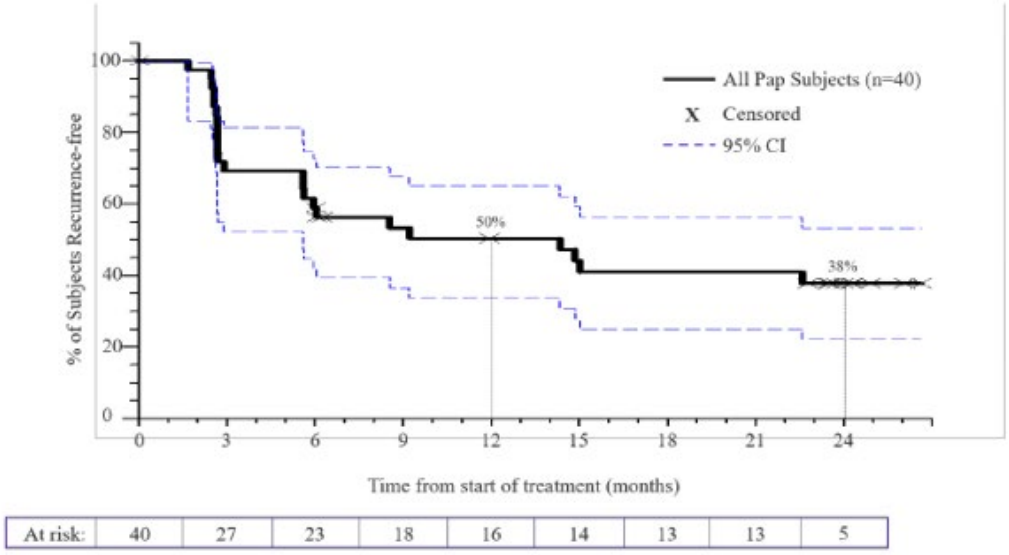
Visit Time from Start of Treatment	CIS Alone	CIS + Ta	CIS + T1	All CIS
mITT	(N=63)	(N=14)	(N=16)	(N=93)
3 Months (95% CI)[1]	37% (23/63) (25%, 50%)	43% (6/14) (18%, 71%)	44% (7/16) (20%, 70%)	39% (36/93) (29%, 49%)
6 Months (95% CI)[1]	27% (17/63) (17%, 40%)	43% (6/14) (18%, 71%)	19% (3/16) (4%, 46%)	28% (26/93) (19%, 38%)
9 Months (95% CI)[1]	19% (12/63) (10%, 31%)	36% (5/14) (13%, 65%)	13% (2/16) (2%, 38%)	20% (19/93) (13%, 30%)
12 Months (95% CI)[1]	16% (10/63) (8%, 27%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	16% (15/93) (9%, 25%)
15 Months (95% CI)[1]	13% (8/63) (6%, 23%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	14% (13/93) (8%, 23%)
18 Months (95% CI)[1]	13% (8/63) (6%, 23%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	14% (13/93) (8%, 23%)
21 Months (95% CI)[1]	11% (7/63) (5%, 22%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	13% (12/93) (7%, 21%)
24 Months (95% CI)[1]	10% (6/63) (4%, 20%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	12% (11/93) (6%, 20%)
Evaluable	(N=59)	(N=14)	(N=16)	(N=89)
3 Months (95% CI)[1]	39% (23/59) (27%, 53%)	43% (6/14) (18%, 71%)	44% (7/16) (20%, 70%)	40% (36/89) (30%, 51%)
6 Months (95% CI)[1]	29% (17/59) (18%, 42%)	43% (6/14) (18%, 71%)	19% (3/16) (4%, 46%)	29% (26/89) (20%, 40%)
9 Months (95% CI)[1]	20% (12/59) (11%, 33%)	36% (5/14) (13%, 65%)	13% (2/16) (2%, 38%)	21% (19/89) (13%, 31%)
12 Months (95% CI)[1]	17% (10/59) (8%, 29%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	17% (15/89) (10%, 26%)
15 Months (95% CI)[1]	14% (8/59) (6%, 25%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	15% (13/89) (8%, 24%)
18 Months (95% CI)[1]	14% (8/59) (6%, 25%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	15% (13/89) (8%, 24%)
21 Months (95% CI)[1]	12% (7/59) (5%, 23%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	13% (12/89) (7%, 22%)
24 Months (95% CI)[1]	10% (6/59) (4%, 21%)	21% (3/14) (5%, 51%)	13% (2/16) (2%, 38%)	12% (11/89) (6%, 21%)

Time to Disease Recurrence in Papillary Disease Subjects:

Table 18: Overall Time to Disease Recurrence[1]: mITT Population Cohort 3

	Cohort 3: Papillary Disease (N=40)
Kaplan-Meier Estimate (days)	
N (Number Censored)	40 (17)
Mean (SE)	386.1 (45.02)
Median (95% CI)	436.0 (170.0, NA)

Figure 2: Kaplan-Meier Plot: Time to Disease Recurrence for Subjects with High-grade Ta or any Grade T1 papillary disease (Cohort 3)

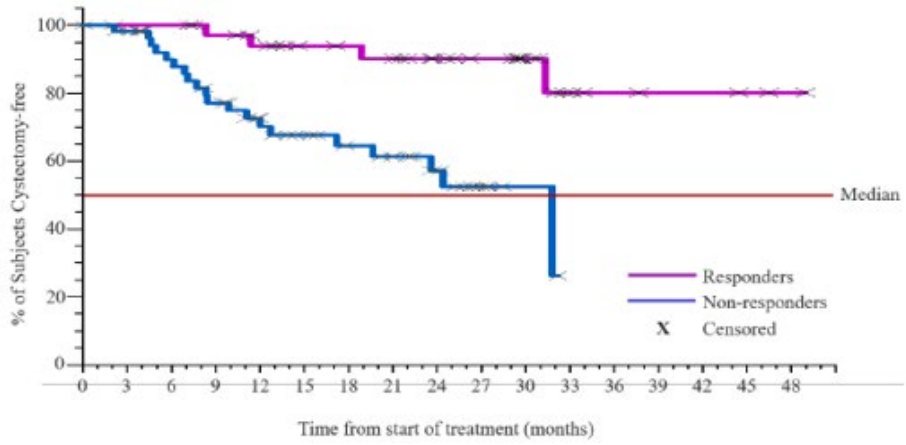


For the papillary disease group with 40 subjects (cohort 3) the overall median time to disease recurrence is 436 days. However, a substantial number of patients have been censored. The results listed in source Table 14.2.5.1.1. are not understood. The applicant is requested to clarify.

In a retrospective study evaluating the clinicopathologic and outcome features of 85 patients with high-grade papillary urothelial carcinoma showed that recurrence, progression, and cancer-specific mortality rates were 36.5%, 40%, and 15%, respectively. About half of the cases that reappeared progressed to greater than pTa disease. All cancer-related deaths occurred in the group of patients with progression, whereas patients with recurrence shared similar outcomes to those with no recurrence. Size of the primary tumour was a significant predictor of tumour progression and cancer-specific survival [Chaux A., 2011]. It shows that the knowledge of progressive disease is of utmost importance to predict the risk for developing cancer-specific death. It is therefore of clinical interest to distinguish between recurrence and progression and this demands a longer follow-up of at least 3 years. The applicant should clarify and elaborate on this and provide updated data containing this distinction.

Time to cystectomy in CIS subjects:

Figure 3: Time to Cystectomy: All CIS Subjects by Response Status at 3 months



Responders at risk:	36	36	36	33	30	26	25	24	19	15	11	6	4	3	3	2	1
Non-responders at risk:	57	53	43	36	29	24	20	17	13	6	2	0	0	0	0	0	0

Figure 3 shows the Kaplan-Meyer plot comparing the group of subjects achieved CR with the group that did not achieve CR in terms of time to cystectomy. Time to cystectomy is a clinically meaningful secondary endpoint. However, it is noted that this analysis was not controlled for multiplicity and is conditioned on response. Furthermore, it is not reliable to use the date of cystectomy in this time line because it can be influenced by different types of incidents and therefore differences in the curve cannot be attributed to treatment effect. The time endpoint should instead be "hard" as e.g. date of biopsy with recurrence. The applicant is requested to present data on date of biopsy with recurrence and discuss the results. Furthermore, the applicant is requested to provide (if available) data on "time to fulfillment of eligibility criteria for cystectomy", rather than the actual surgery for the CIS population.

All tables provided of time to event endpoints (DoR, EFS, PFS, OS, Time to Disease Recurrence in Papillary Disease Subject, time to cystectomy, etc.) include only the number of censored subjects. For completeness, the number of events (and type of event) as well as reasons for censoring should be included.

Efficacy data included in section 5.1 of the SmPC should be limited to those from the Phase 3 pivotal study. Study VB4-845-IIA is considered supportive.

Event-free Survival (EFS) in all subjects:

Table 19: Event-free Survival: Overall miTT Population

	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=86)	Cohort 2: CIS With or Without Papillary Disease Within 6 – 11 mo of BCG (N=7)	Cohort 1 + Cohort 2: All CIS With or Without Papillary Disease (N=93)	Cohort 3: Papillary Disease (N=40)	Overall (N=133)
Kaplan-Meier Estimate (days)					
N (Number Censored)	86 (15)	7 (2)	93 (17)	40 (17)	133 (34)
Mean (SE)	257.4 (36.08)	223.3 (55.11)	266.9 (35.37)	386.1 (44.32)	339.8 (33.80)
Median (95% CI)	81.0 (80.0, 93.0)	246.0 (78.0, NA)	81.0 (80.0, 168.0)	436.0 (170.0, NA)	90.5 (81.0, 179.0)
25%-75%	79.0-233.0	79.0-360.0	79.0-260.0	81.0-NA	79.0-452.0
Min, Max	1, 1018	78, 723	1, 1018	1, 810	1, 1018

Seagen Bio
VB-845-02-IIIA
24 Month Follow-Up Analysis

Table 14.2.3.1.1
Event-Free Survival [1]
Overall
miTT Population

	CIS With or Without Papillary Disease Within 6 mo of BCG (N=86)			CIS With or Without Papillary Disease Within 6 - 11 mo of BCG (N=7)			Total CIS With or Without Papillary Disease (N=93)		
	Subjects At Risk	Cum Events	KM% (95% CI)	Subjects At Risk	Cum Events	KM% (95% CI)	Subjects At Risk	Cum Events	KM% (95% CI)
Overall									
Week 1 (Day 1 - 7)	86 (100%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	93 (100%)	0	100 (100, 100)
Week 2 (Day 8 - 14)	82 (95%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	89 (96%)	0	100 (100, 100)
Week 3 (Day 15 - 21)	82 (95%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	89 (96%)	0	100 (100, 100)
Week 4 (Day 22 - 28)	82 (95%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	89 (96%)	0	100 (100, 100)
Week 5 (Day 29 - 35)	82 (95%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	89 (96%)	0	100 (100, 100)
Week 6 (Day 36 - 42)	82 (95%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	89 (96%)	0	100 (100, 100)
Week 7 (Day 43 - 49)	82 (95%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	89 (96%)	0	100 (100, 100)
Week 8 (Day 50 - 56)	82 (95%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	89 (96%)	0	100 (100, 100)
Week 9 (Day 57 - 63)	82 (95%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	89 (96%)	0	100 (100, 100)
Week 10 (Day 64 - 70)	82 (95%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	89 (96%)	0	100 (100, 100)
Week 11 (Day 71 - 77)	82 (95%)	3	96 (89, 99)	7 (100%)	0	100 (100, 100)	89 (96%)	3	97 (90, 99)
Week 12 (Day 78 - 84)	79 (92%)	45	45 (34, 55)	7 (100%)	3	57 (17, 84)	86 (92%)	48	46 (35, 56)
Week 13 (Day 85 - 91)	37 (43%)	49	40 (30, 51)	4 (57%)	3	57 (17, 84)	41 (44%)	52	42 (31, 52)

Note: An event in subjects with CIS with or without papillary disease is defined as persistent high-grade disease or recurrence of CIS or high-grade papillary disease after achieving a complete response. An event in subjects with papillary disease alone is defined as recurrence of papillary disease of high-grade Ta or T1 disease or low-grade T1 (if baseline disease), or development of CIS. Tumor recurrence, tumor progression to muscle invasive bladder cancer, discontinuation due to treatment failure or recurrence, or death prior to treatment discontinuation are considered events in either group.
[1] Event-free survival--defined as the number of days from the date of first dose of study treatment to an event--is estimated using the method of Kaplan-Meier. Subjects with a treatment failure at their post-Induction Phase assessment will be considered to have a treatment failure at the time of the assessment. Subjects without evidence of a treatment failure who receive a new anti-cancer therapy or who have a second non-NMIBC cancer are censored at the date of the last evaluable disease assessment on or prior to the date of treatment or diagnosis. Subjects without evidence of a treatment failure who undergo cystectomy will be censored at the date of cystectomy. All other subjects will be censored at the time of last assessment.
Source: ...\VB-845-02-IIIA\Programs\Analysis\Production\Tables\Final Analysis\t_km.sas, Date/time of run: 06NOV2020:20:22

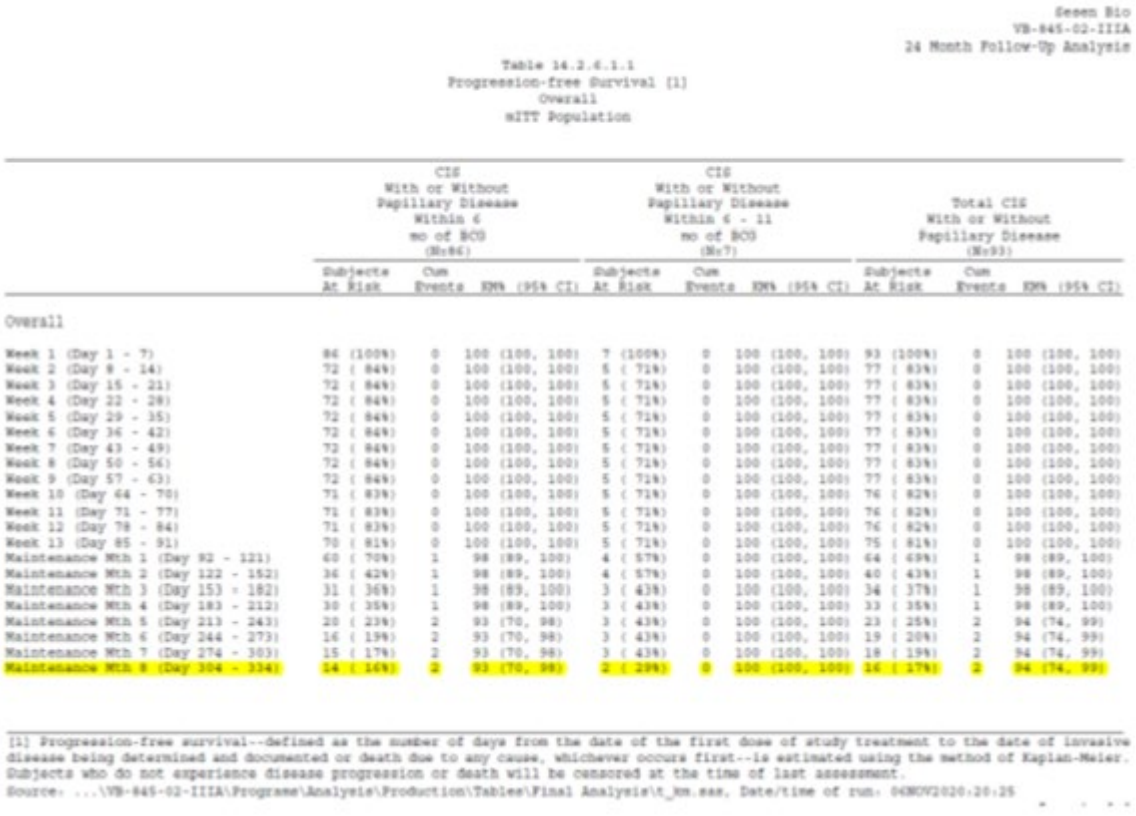
Page 1 of 9

The applicant should provide an EFS curve for the Cohort 1 + 2.

Progressions-Free Survival (PFS):

Table 20: Progression-Free Survival: Overall miTT Population

	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=86)	Cohort 2: CIS With or Without Papillary Disease Within 6 – 11 mo of BCG (N=7)	Cohort 1 + Cohort 2: All CIS With or Without Papillary Disease (N=93)	Cohort 3: Papillary Disease (N=40)	Overall (N=133)
Kaplan-Meier Estimate (days)					
N (Number Censored)	86 (84)	7 (7)	93 (91)	40 (39)	133 (130)
Mean (SE)	219.8 (3.07)	NE (NE)	220.0 (2.87)	472.0 (NE)	461.2 (9.43)
Median (95% CI)	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)	NA (NA, NA)
25%-75%	NA - NA	NA - NA	NA - NA	NA - NA	NA - NA
Min, Max	1, 1149	1, 766	1, 1149	1, 946	1, 1149



Seagen Bio
VB-845-02-IIIA
24 Month Follow-Up Analysis

Table 14.2.6.1.1
Progression-free Survival [1]
Overall
mITT Population

	CIS With or Without Papillary Disease Within 6 mo of BCG (N=86)			CIS With or Without Papillary Disease Within 6 - 11 mo of BCG (N=7)			Total CIS With or Without Papillary Disease (N=93)		
	Subjects At Risk	Cum Events	KM% (95% CI)	Subjects At Risk	Cum Events	KM% (95% CI)	Subjects At Risk	Cum Events	KM% (95% CI)
Overall									
Week 1 (Day 1 - 7)	86 (100%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	93 (100%)	0	100 (100, 100)
Week 2 (Day 8 - 14)	72 (84%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	77 (83%)	0	100 (100, 100)
Week 3 (Day 15 - 21)	72 (84%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	77 (83%)	0	100 (100, 100)
Week 4 (Day 22 - 28)	72 (84%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	77 (83%)	0	100 (100, 100)
Week 5 (Day 29 - 35)	72 (84%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	77 (83%)	0	100 (100, 100)
Week 6 (Day 36 - 42)	72 (84%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	77 (83%)	0	100 (100, 100)
Week 7 (Day 43 - 49)	72 (84%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	77 (83%)	0	100 (100, 100)
Week 8 (Day 50 - 56)	72 (84%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	77 (83%)	0	100 (100, 100)
Week 9 (Day 57 - 63)	72 (84%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	77 (83%)	0	100 (100, 100)
Week 10 (Day 64 - 70)	71 (83%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	76 (82%)	0	100 (100, 100)
Week 11 (Day 71 - 77)	71 (83%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	76 (82%)	0	100 (100, 100)
Week 12 (Day 78 - 84)	71 (83%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	76 (82%)	0	100 (100, 100)
Week 13 (Day 85 - 91)	70 (81%)	0	100 (100, 100)	5 (71%)	0	100 (100, 100)	75 (81%)	0	100 (100, 100)
Maintenance Mth 1 (Day 92 - 121)	60 (70%)	1	98 (89, 100)	4 (57%)	0	100 (100, 100)	64 (69%)	1	98 (89, 100)
Maintenance Mth 2 (Day 122 - 152)	36 (42%)	1	98 (89, 100)	4 (57%)	0	100 (100, 100)	40 (43%)	1	98 (89, 100)
Maintenance Mth 3 (Day 153 - 182)	31 (36%)	1	98 (89, 100)	3 (43%)	0	100 (100, 100)	34 (37%)	1	98 (89, 100)
Maintenance Mth 4 (Day 183 - 212)	30 (35%)	1	98 (89, 100)	3 (43%)	0	100 (100, 100)	33 (35%)	1	98 (89, 100)
Maintenance Mth 5 (Day 213 - 243)	20 (23%)	2	93 (70, 98)	3 (43%)	0	100 (100, 100)	23 (25%)	2	94 (74, 99)
Maintenance Mth 6 (Day 244 - 273)	16 (19%)	2	93 (70, 98)	3 (43%)	0	100 (100, 100)	19 (20%)	2	94 (74, 99)
Maintenance Mth 7 (Day 274 - 303)	15 (17%)	2	93 (70, 98)	3 (43%)	0	100 (100, 100)	18 (19%)	2	94 (74, 99)
Maintenance Mth 8 (Day 304 - 334)	14 (16%)	2	93 (70, 98)	2 (29%)	0	100 (100, 100)	16 (17%)	2	94 (74, 99)

[1] Progression-free survival--defined as the number of days from the date of the first dose of study treatment to the date of invasive disease being determined and documented or death due to any cause, whichever occurs first--is estimated using the method of Kaplan-Meier. Subjects who do not experience disease progression or death will be censored at the time of last assessment.
Source: ...\VB-845-02-IIIA\Programs\Analysis\Production\Tables\Final Analysis\t_km.sas, Date/time of run: 04NOV2020:20:25

Regarding the progression-free survival (PFS) for the mITT population table 20 shows that the median was not reached. The interpretation of time-to-event endpoints is hampered by the study design.

The applicant states: "More than 90% of the mITT population remained progression-free at their last assessment (CSR, page 85). This statement is not understood. According to Table 14.2.6.1.1 (page

429 in Appendix 14), only 2 PFS events were reported by maintenance week Month 8. The applicant is requested to clarify this statement.

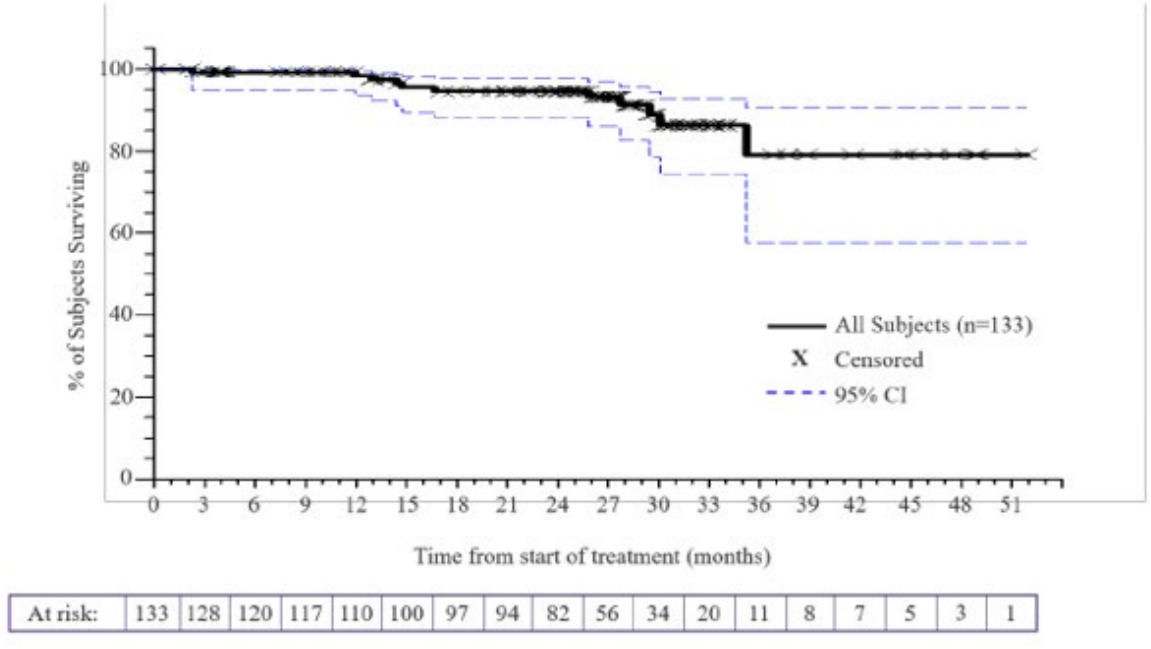
The applicant should provide a PFS curve for the Cohort 1 + 2.

Overall Survival (OS) in all subjects:

Table 21: Overall Survival: miTT Population

	Cohort 1: CIS With or Without Papillary Disease Within 6 months of BCG (N=86)	Cohort 2: CIS With or Without Papillary Disease Within 6 – 11 mo of BCG (N=7)	Cohort 1 + Cohort 2: All CIS With or Without Papillary Disease (N=93)	Cohort 3: Papillary Disease (N=40)	Overall (N=133)
Kaplan-Meier Estimate (days)					
N (Number Censored)	86 (76)	7 (7)	93 (83)	40 (39)	133 (122)
Mean (SE)	988.1 (27.41)	NE (NE)	994.6 (25.36)	915.0 (NE)	1017.0 (17.44)
Median (95% CI)	NA (1071.0, NA)	NA (NA, NA)	NA (1071.0, NA)	NA (NA, NA)	NA (NA, NA)
25%-75%	1071.0 - NA	NA - NA	1071.0 - NA	NA - NA	NA - NA
Min, Max	2, 1489	521, 1031	2, 1489	76, 1577	2, 1577

Figure 4: Kaplan-Meier Plot: Overall Survival



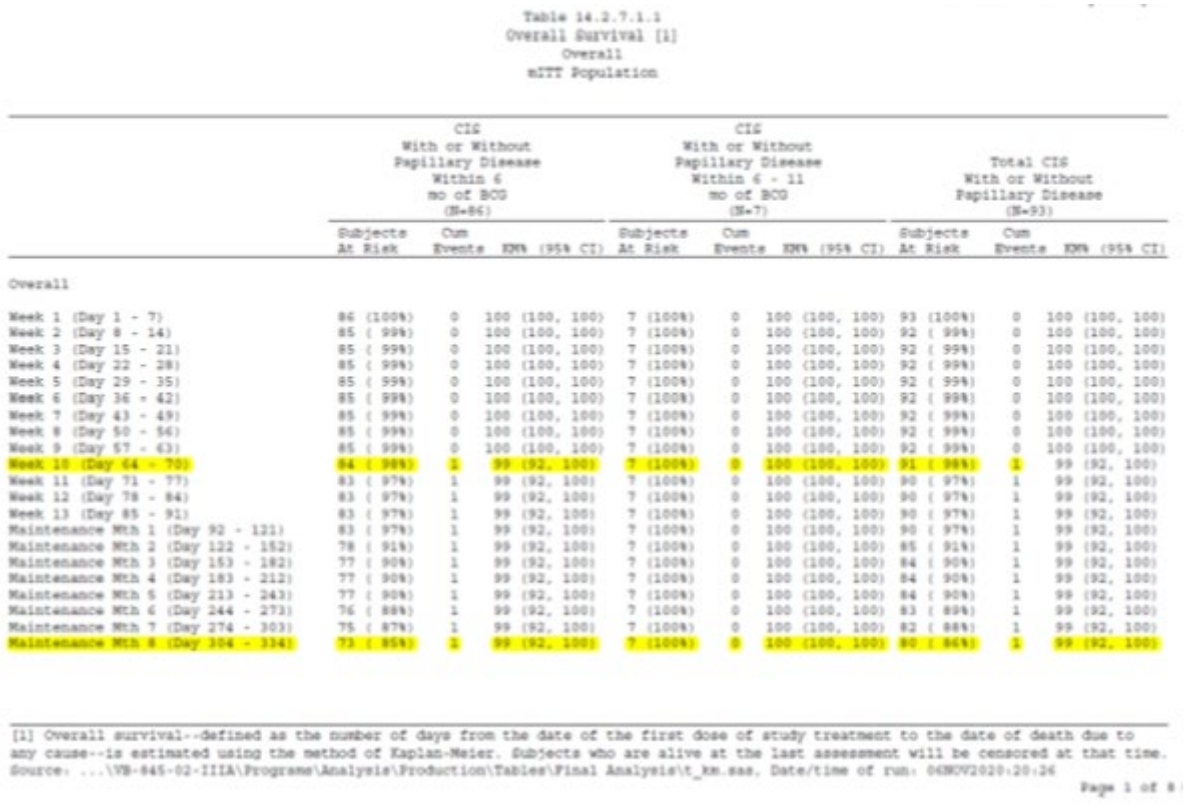


Table 14.2.7.1.1
Overall Survival [1]
Overall
mITT Population

	CIS With or Without Papillary Disease Within 6 mo of BCG (N=86)			CIS With or Without Papillary Disease Within 6 - 11 mo of BCG (N=7)			Total CIS With or Without Papillary Disease (N=93)		
	Subjects At Risk	Cum Events	KMN (95% CI)	Subjects At Risk	Cum Events	KMN (95% CI)	Subjects At Risk	Cum Events	KMN (95% CI)
Overall									
Week 1 (Day 1 - 7)	86 (100%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	93 (100%)	0	100 (100, 100)
Week 2 (Day 8 - 14)	85 (99%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	92 (99%)	0	100 (100, 100)
Week 3 (Day 15 - 21)	85 (99%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	92 (99%)	0	100 (100, 100)
Week 4 (Day 22 - 28)	85 (99%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	92 (99%)	0	100 (100, 100)
Week 5 (Day 29 - 35)	85 (99%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	92 (99%)	0	100 (100, 100)
Week 6 (Day 36 - 42)	85 (99%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	92 (99%)	0	100 (100, 100)
Week 7 (Day 43 - 49)	85 (99%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	92 (99%)	0	100 (100, 100)
Week 8 (Day 50 - 56)	85 (99%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	92 (99%)	0	100 (100, 100)
Week 9 (Day 57 - 63)	85 (99%)	0	100 (100, 100)	7 (100%)	0	100 (100, 100)	92 (99%)	0	100 (100, 100)
Week 10 (Day 64 - 70)	84 (98%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	91 (98%)	1	99 (92, 100)
Week 11 (Day 71 - 77)	83 (97%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	90 (97%)	1	99 (92, 100)
Week 12 (Day 78 - 84)	83 (97%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	90 (97%)	1	99 (92, 100)
Week 13 (Day 85 - 91)	83 (97%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	90 (97%)	1	99 (92, 100)
Maintenance Mth 1 (Day 92 - 121)	83 (97%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	90 (97%)	1	99 (92, 100)
Maintenance Mth 2 (Day 122 - 152)	78 (91%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	85 (91%)	1	99 (92, 100)
Maintenance Mth 3 (Day 153 - 182)	77 (90%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	84 (90%)	1	99 (92, 100)
Maintenance Mth 4 (Day 183 - 212)	77 (90%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	84 (90%)	1	99 (92, 100)
Maintenance Mth 5 (Day 213 - 243)	77 (90%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	84 (90%)	1	99 (92, 100)
Maintenance Mth 6 (Day 244 - 273)	76 (88%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	83 (89%)	1	99 (92, 100)
Maintenance Mth 7 (Day 274 - 303)	75 (87%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	82 (88%)	1	99 (92, 100)
Maintenance Mth 8 (Day 304 - 334)	73 (85%)	1	99 (92, 100)	7 (100%)	0	100 (100, 100)	80 (86%)	1	99 (92, 100)

[1] Overall survival--defined as the number of days from the date of the first dose of study treatment to the date of death due to any cause--is estimated using the method of Kaplan-Meier. Subjects who are alive at the last assessment will be censored at that time.
Source: ...\VB-845-02-IIIA\Programs\Analysis\Production\Tables\Final Analysis\t_km.sas, Date/time of run: 04NOV2020:20:26

Page 1 of 8

The applicant is requested to present for OS a table indicating by timepoint which patients had an event, which were censored and the reason for censoring for all included study patients.

The interpretation of time-to-event endpoints is hampered by the study design. OS is not relevant in NMIBC as there is a curative option with RC or radiotherapy which can provide intervention prior to disease progressing to MIBC and becoming lethal, and as emphasised earlier patients who developed a NMIBC recurrence had similar OS and disease-specific survival (DSS) to those who did not.

Ancillary analyses

EpCAM Expression

According to the dossier an immunohistochemistry (IHC) assay developed and validated for screening of subject biopsies of squamous cell carcinoma of the head and neck (SCCHN) was used to analyse the distribution of EpCAM expression. It was done retrospectively in the pivotal study. According to the applicant the expression was high trough out the 3 studies. There was no correlation between the response outcome and either the overall EpCAM score or the percentage of tumour cells staining positive for EpCAM.

However, no tables with the results of the EpCAM expressions could be found in the dossier. The applicant should provide further data showing efficacy as function of EpCAM expression levels.

Scientific rationale for the choice of the predictive *in vitro* biomarker test (e.g. prevalence, relation to disease mechanism) should be provided.

Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method should be provided.

For the analytical and clinical validation strategy, the applicant should provide:

- Analytical validity: For verifying the suitability of an assay, robustness, accuracy, specificity, sensitivity and linearity should be considered depending on the analytical platform

- Clinical validity (sensitivity/specificity) should be described either by correlation with a clinical endpoint (for novel assays) or –if available- by concordance study with a clinically valid reference assay

- Cut-point selection should be described and discussed in detail since it is of particular importance for the benefit /risk assessment.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 22: Summary of efficacy for trial VB4-845-02-IIIA

Title: An Open-Label, Multicenter, Phase 3 Study to Evaluate the Efficacy and Tolerability of Intravesical Vicinium™ in Subjects with Non-Muscle-Invasive Carcinoma in Situ (CIS) and/or High-Grade Papillary Disease of the Bladder Previously Treated with Bacillus Calmette-Guérin (BCG).			
Study identifier	VB4-845-02-IIIA NCT02449239		
Design	Open-label, multicentre, phase III study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 months NA NA
Hypothesis	Exploratory: Other - CR at 3 months, the 95% CI excludes 20%		
Treatments groups	Cohort 1 Subjects with CIS with and without associated papillary disease (PD < 6		Induction phase for 12 weeks/maintenance phase for up to 92 weeks/follow-up phase Total numbers randomised:86
	Cohort 2 Subjects with CIS with and without associated papillary disease (PD<11 months)		Same treatment Total number randomised: 7
	Cohort 3 Subjects with papillary disease		Same treatment Total number randomised:40
Endpoints and definitions	Primary endpoint	Complete response rate (CR) at 3 months Cohort 1+2	Subjects with CIS were considered to have CR if at assessment after 3 months there is no evidence of high-grade disease or disease progression.
	Primary endpoint	Duration of response (DoR) Cohort 1+2	DoR was for subjects analysed in cohort 1+2 who achieved a CR at the 3 months assessment.

	Secondary endpoint	CR at 3, 6, 9, 12, 15, 18 and 24 months (Cohort 1+2)	See primary endpoint
	Secondary endpoint	Disease recurrence free (RF), time to recurrence	Time to disease recurrence is defined as number of days from first dose to the first occurrence of treatment failure or death.
Database lock	6 october 2020		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point	Modified intent-to-treat population (mITT) includes subject who received at least one dose of study treatment. This is the primary population for efficacy and safety.		
Complete response	Treatment group	Cohort 1+2	Cohort 3
	Number of subjects	86+7	40
	CR at 3 months (95% at CI)	39% (36/93) (29%, 49%)	NA
	CR at 6 months	28% (26/93) (19%, 38%)	NA
	CR at 9 months	20% (19/93) (13%, 30%)	NA
	CR at 12 months	16% (15/93) (9%, 25%)	NA
	CR at 15 months	16% (15/93) (13%, 30%)	NA
	CR at 18 months	14% (13/93) (8%, 23%)	NA
	CR at 21 months	NA	13% (12/93) (7%, 21%)
	CR at 24 months	NA	12% (11/93) (6%, 20%)

Recurrence free survival	Month 3	NA	68% (27/40) (51%, 81%)
	Month 6	NA	55% (22/40) (38%, 71%)
	Month 9	NA	43% (17/40) (27%, 59%)
	Month 12	NA	43% (17/40) (27%, 59%)
	Month 15	NA	33% (13/40) (19%, 49%)
	Month 18	NA	33% (13/40) (19%, 49%)
	Month 21	NA	33% (13/40) (19%, 49%)
	Month 24	NA	30% (12/40) (17%, 47%)

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

No special subject populations were evaluated. As the eligibility criteria required subjects to have adequate renal and hepatic function, specific subgroup analyses of subjects with renal or hepatic impairment in the targeted subject population were not feasible.

The following table, though should be provided as part of the answers to the day 120 LoQ.

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials			
Non Controlled trials			

Supportive studies

The two supportive studies are the VB4-845-02-I study (Phase 1/2) and the VB4-845-02-IIA study (Phase 2).

VB4-845-02-I

Table 23: Response as assessed by post hoc analysis by dose group

Response as Assessed by Algorithm	Number of Patients (%)			
	0.1 mg - < 1.0 mg (N=17)	1.0 mg - < 10.0 mg (N=14)	≥ 10.0 mg (N=33)	Total (N=64)
Complete response	3(17.6)	7(50.0)	15(45.5)	25(39.1)
Partial response	6(35.3)	2(14.3)	10(30.3)	18(28.1)
Stable disease	5(29.4)	3(21.4)	6(18.2)	14(21.9)
Tumour progression	2(11.8)	1(7.1)	1(3.0)	4(6.3)
Missing assessment	1(5.9)	1(7.1)	1(3.0)	3(4.7)

Data source Listing 16.2.6.4

Table 24: Response as assessed by post hoc analysis by baseline tumour classification and tumour analysis group

Tumour Classification at Baseline	Response				
	Complete Response	Partial Response	Stable Disease	Tumour Progression	Missing Assessment
Tis (N=17)	5(29.4)	5(29.4)	6(35.3)	0	1(5.9)
T1 (N=17)	7(41.2)	6(35.3)	1(5.9)	1(5.9)	2(11.8)
Ta (N=30)_	13(43.3)	7(23.3)	7(23.3)	3(10.0)	0
Total (N=64)	25(39.1)	18(28.1)	14(21.9)	4(6.3)	3(4.7)
Tumour Analysis Group at Baseline					
Tis (N=17)	5(29.4)	5(29.4)	6(35.3)	0	1(5.9)
Ta /T1 disease resected (N=45)	20(44.4)	12(26.7)	7(15.6)	4(8.9)	2(4.4)
Ta/T1 disease visible lesions (N=2)	0	1(50.0)	1(50.0)	0	0
Total (N=64)	25(39.1)	18(28.1)	14(21.9)	4(6.3)	3(4.7)

Since the MTD was not reached with the original dose escalation design in the Phase 1 Part of this Phase 1/2 study, the dose escalation scheme was amended and Part 2 of the study was not conducted. The protocol was amended 5 times with significant changes to the protocol regarding dose levels, number of subjects, treatment schemes and baseline characteristics of the subjects. In total 64 subjects were enrolled in 3 dose levels with the greatest number of subjects in the highest dose group.

Subjects in the highest dose group seem to experience the best ORR and fewer had PD compared with the subjects on the 2 other dose levels. Response assessed by tumour classification is not possible to interpret due to few subjects.

VB4-845-02-IIA

Table 25: Previous Anti-Tumour Treatment for Bladder Cancer – miTT Population*

Previous Anti-Tumour Treatment	Treatment Schedule A (N=22)	Treatment Schedule B (N=23)	Total (N=45)
Chemotherapy, n (%)	0	1 (4.3)	1 (2.2)
Failed to respond	0	1 (100.0)	1 (100.0)
BCG, n (%)	22 (100.0)	23 (100.0)	45 (100.0)
Complete	0	2 (8.7)	2 (4.4)
Partial	2 (9.1)	2 (8.7)	4 (8.9)
Failed to respond	18 (81.8)	15 (65.2)	33 (73.3)
Intolerant	2 (9.1)	4 (17.4)	6 (13.3)
TURBT, n (%)	17 (77.3)	19 (82.6)	36 (80.0)
Complete	1 (5.9)	3 (15.8)	4 (11.1)
Partial	4 (23.5)	5 (26.3)	9 (25.0)
Failed to respond	12 (70.6)	10 (52.6)	22 (61.1)
Other, n (%)	6 (27.3)	3 (13.0)	9 (20.0)
Complete	3 (50.0)	1 (33.3)	4 (44.4)
Partial	1 (16.7)	1 (33.3)	2 (22.2)
Failed to respond	2 (33.3)	1 (33.3)	3 (33.3)

Data source: Table 3.5.5

Table 26: NHED and NED Response Rates – mITT Population

Timepoint (Schedule A, Schedule B)	Treatment Schedule A (N=22) n (%)	Treatment Schedule B (N=23) n (%)	Total (N=45) n (%)
Weeks 12, 13			
Number of subjects[a]	22	23	45
Total complete response	9 (40.9)	9 (39.1)	18 (40.0)
NHED	2 (9.1)	6 (26.1)	8 (17.8)
NED	7 (31.8)	3 (13.0)	10 (22.2)
Complete response at any timepoint			
Number of subjects[a,b]	22	23	45
Total complete response	11 (50.0)	9 (39.1)	20 (44.4)
NHED	3 (13.6)	6 (26.1)	9 (20.0)
NED	8 (36.4)	3 (13.0)	11 (24.4)

Data source: Table 3.6.1

NED = no evidence of disease; NHED = no histological evidence of disease

Note: Percentages are based on the number of subjects who had non-missing responses in the mITT population.

a. Subject 1102 (Treatment Schedule A) received only 1 dose of study medication and discontinued prior to the first Week 12 assessment.

[redacted]

Forty-six subjects were enrolled in the Phase 2 study with 45 subjects included in the mITT population. All subjects had CIS with 20% having coexisting papillary disease. 40.9% and 39.1% achieved a complete response in treatment schedule A and B, respectively. Two and 7 subjects in A and B, respectively, achieved a pCR. These results are consistent with what was seen in the pivotal study. However, the data should be assessed with precaution as only 10/45 subjects had received adequate BCG dosing.

3.3.6. Discussion on clinical efficacy

The clinical efficacy data supporting this marketing authorisation request rely on one pivotal study VB4-845-02-IIIA, an open-label, non-randomised, multicentre study in subjects with BCG-unresponsive Non-Muscle-Invasive bladder cancer (NMIBC).

Oportazumab monatox is a novel pharmacologic class that specifically binds to EpCAM, a cell-surface antigen overexpressed on a wide variety of epithelial-derived cancer cells including urothelial carcinomas that have been shown to overexpress EpCAM with limited expression on normal epithelium. The specific binding of EpCAM on urothelial cancers by VB4-845 preferentially targets and kills these cancer cells while sparing normal urothelium. The dose selection was partly based on a phase 1/2 study and a subsequent phase 2 study.

The applicant is seeking a MA for the following *proposed indications*:

• the treatment and prevention of recurrence of carcinoma in situ (CIS) of the urinary bladder following transurethral resection in BCG-unresponsive patients.

• the prevention of recurrence of high-grade Ta and/or T1 papillary tumours following transurethral resection in BCG-unresponsive patients.

In study VB4-845-02-IIIA studied is BCG-unresponsive subjects with CIS with and without associated papillary disease and patients with high-grade Ta and/or T1 papillary tumours alone following TURBT, were recruited. This is reflected in the wording of the sought indication which is however not endorsed since:

a) only subjects with urothelial cancer histology were included in the pivotal study.

b) the wording is not reflective of the study design, since evidence for preventing development of disease requires not only absence of disease at baseline but also interpretation of time-dependent endpoints which is not possible in the absence of a comparator. With this in mind it is not possible to isolate the treatment effect of oportuzumab monatox in preventing recurrence of high-grade Ta and/or T1 papillary tumours (i.e. the second part of the indication).

c) as mentioned, the pivotal study is a "treatment" study where histologically proven CIS is present in all subjects in cohort 1+2 at baseline, rather than a prophylaxis study where disease would need to have been previously resected. An indication for the prevention of recurrence of CIS is therefore not supported.

Taking all the above into account the wording of the indication should be modified. The following wording is proposed:

"Oportuzumab monatox as monotherapy is indicated for the treatment of Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumours in adult patients, following transurethral resection".

According to the dossier an immunohistochemistry (IHC) assay developed and validated for screening of subject biopsies of squamous cell carcinoma of the head and neck (SCCHN) was used to analyse the distribution of EpCAM expression. It was done retrospectively in the pivotal study. According to the applicant the expression was high trough out the 3 studies. There was no correlation between the response outcome and either the overall EpCAM score or the percentage of tumour cells staining positive for EpCAM. However, no tables with the results of the EpCAM expressions could be found in the dossier. The applicant should provide further data showing efficacy as function of EpCAM expression levels.

Design and conduct of clinical studies

Scientific advice from the CHMP was received for the first time in 2009. The CHMP did not consider it adequate to use an open-label single arm study to support conditional/full MA. The CHMP stated in the SA "In conclusion, the Company is advised to proceed to the randomised controlled trial based on the phase II results available and not to divert patients into an uncontrolled trial that is likely to be at most only supportive." The applicant chose not to follow the advice given by the CHMP.

The design and conduct of the pivotal study are not considered adequate for a pivotal study:

a) The expected effect size or efficacy hypothesis of the study was not mentioned in the protocol. It was neither described which was the response criterium required to consider the study successful. According to the original sample size calculation, the CR obtained at 12 months was expected to be larger than 20 %. The CR at 12 months observed in the current study is (Cohort 1 + 2) 16.1 % with 95 % CI (9.3 %; 25.2%) (Assessor's own calculations). The applicant is requested to clarify why the study is considered successful**.**

b) The primary endpoint was changed 3 times during the course of the study and the wording differs between the protocol amendment 3 and the CSR. In particular, in the protocol CR at 6 months is implemented with CR at 3 months was reported in the CSR. The applicant is asked to clarify why the primary endpoint was changed while the study was ongoing and the use of CR at 3 months as primary endpoint.

c) The study is not controlled for multiplicity for neither primary nor secondary endpoints. The applicant is requested to justify this approach in a pivotal study

According to the sample size, a minimum of 77 evaluable subjects would be needed to exclude a CR rate at 12 months of 20 %. This is applicable to the first version of the protocol. However, the primary endpoint was changed but the sample size calculations were not revised. It is not understood why the CR at 12 months was used for the sample size calculations when the primary endpoint was CR at 3 months. Thus, the power of the study for the primary endpoint is unknown. Assuming that the number of responders at 3 months is higher than at 12 months, the study is expected to be powered to exclude a lower bound of the 95 % CI of CR at 3 months of 20 %. It is also unclear why the study was powered for a secondary endpoint which was not controlled for multiplicity. The sample size calculation does not seem taken into account study discontinuation, initiation of another therapy before progression, or RC. In conclusion, the presented sample size is not relevant to the current study.

The clinical relevance of the primary endpoint, the short follow-up time and the duration of effect is questioned. The applicant is requested to discuss and justify the following:

a) Recently established complete response benchmarks for new therapies for BCG unresponsive CIS were developed according to AUA/FDA workshop recommendations. A clinically meaningful initial complete response rate (for CIS) or recurrence-free rate (for papillary tumours) of at least 50% at 6 months, 30% at 12 months and 25% at 18 months is recommended. The results of the pivotal study seem not to be in line with these complete response benchmarks. Hence, oportuzumab showed a lack of clinically relevant treatment effect with a poor complete response rate of 16% (CIS) at the originally endpoint of 12 months. A placebo response rate in the current setting is likely. CIS is present at baseline, and sensitivity less than 100% for follow-up cystoscopy with biopsy will fail to find CIS in some patients (e.g. 1 - sensitivity). Accordingly, even if no therapy had been administered, a fraction of patients would be deemed responders (= placebo response rate). Accordingly, unlike ORR, the entire of the CR seen cannot be attributed to drug effect. Please discuss and justify that efficacy has been isolated and thereby scientifically established.

b) Oportuzumab monatox has shown activity in patients with NMIBC with CIS (with or without papillary disease) who are BCG-unresponsive, based on an observed CR rate at 3 months of 39% (36 of 93 patients). However, duration of the effect appears limited, with a median duration of response of approximately 9 months and only 11 patients maintaining the response at 2 years. Whether the observed efficacy results can be expected to translate into clinically meaningful benefit for patients (e.g. a delay in time to cystectomy with no detrimental effect in survival) is uncertain. Further substantiation of the reported data is needed to justify a clinical benefit in the claimed patient population.

c) Retrospective studies show that 24% of CRs developed a NMIBC recurrence after combined-modality therapy (CMT) after mean follow-up of 5.1 years. The median time to first NMIBC recurrence was 19.2 months. Seven (9%) of NMIBC recurrences occurred after 10 years of recurrence-free period. Patients who developed a NMIBC recurrence had similar OS and disease-specific survival (DSS) to those who did not. On multivariate analysis, CIS at the time of MIBC diagnosis was the most important risk factor for NMIBC recurrence [Sanchez A., 2018]. To interpret the data from the pivotal study into clinical meaningfulness demands a longer follow-up than 30 months (see earlier OC). The applicant is requested to discuss the clinical relevance of the primary endpoint and the applicant should discuss and justify the chosen follow-up time together withproviding updated data. A placebo response rate in the current setting is likely. CIS is present at baseline, and sensitivity less than 100% for follow-up cystoscopy with biopsy will fail to find CIS in some patients (e.g. 1 - sensitivity). Accordingly, even if no therapy had been administered, a fraction of patients would be deemed responders (= placebo response rate). Accordingly, unlike ORR, the entire of the CR seen cannot be attributed to drug effect. Please discuss and justify that efficacy has been isolated and thereby scientifically established.

As BCG is still part of the treatment armamentarium because it is efficient and still part of the future clinical trials, it is therefore crucial that the subjects in the pivotal study have been treated with sufficient BCG therapy. The protocol was amended with a new definition of sufficient BCG treatment. A not specified number of subjects may therefore have not been treated sufficiently with BCG before enrolment, which is a point of criticism. According to the baseline characteristics it is not possible to be informed, if the subjects have had other intravesical therapies and which type. The applicant should therefore elaborate more thoroughly on the baseline characteristics.

The conduct of the pivotal study (and also the dose response studies as the matter of fact) with an original protocol as of 03 April 2015 has had several amendments and changes in the inclusion/exclusion criteria, SAP and endpoints. Furthermore, the whole recruiting progress, participant flow, baseline characteristics and numbers analysed are not understood. These uncertainties and concerns about the credibility of data should trigger a GCP inspection.

Efficacy data and additional analyses

The applicant operates with mITT for the primary analysis. However, there is concern regarding the calculation of response rate. All eligible subjects should be included in the denominator for the calculation of the response rate, which was not the case for sCR. To contextualize if the results are clinically meaningful the CRR in subjects with CIS at 3 months was 39% (36/93), at 6 months 28% (26/93), at 12 months 16% (15/93) and at 18 months 14% (13/93). Hence, Oportuzumab showed a lack of clinically relevant treatment effect with a poor complete response rate of 16% (CIS) at the originally endpoint of 12 months.

For the subjects with papillary disease the median time to disease recurrence was 436 days. In a retrospective study evaluating the clinicopathologic and outcome features of 85 patients with high-grade papillary urothelial carcinoma showed that about half of the cases that reappeared progressed to

greater than pTa disease. All cancer-related deaths occurred in the group of patients with progression, whereas patients with recurrence shared similar outcomes to those with no recurrence. Size of the primary tumour was a significant predictor of tumour progression and cancer-specific survival [Chaux A., 2011]. It shows that the knowledge of progressive disease is of utmost importance to predict the risk for developing cancer-specific death. It is therefore of clinical interest to distinguish between recurrence and progression. The applicant should therefore clarify and elaborate on this and provide updated data containing this distinction.

The interpretation of the time-to-event secondary endpoints (DoR, time to cystectomy, EFS, PFS and OS) is hampered by the study design. The censoring rules implemented by the applicant were not fully understood and in many cases not supported. Clarifications and additional analyses are requested. Time to cystectomy is a clinically meaningful secondary endpoint. However, it is not reliable to use the date of cystectomy in this time line because it can be influenced by different types of incidents and therefore biased. The time endpoint should instead be "hard" as e.g. date of biopsy with recurrence. The applicant is requested to present data on date of biopsy with recurrence and discuss the results. Furthermore, the applicant is requested to provide (if available) data on "time to fulfilment of eligibility criteria for cystectomy", rather than the actual surgery for the CIS population. OS is not relevant in NMIBC as there is a curative option with RC or radiotherapy which can provide intervention prior to disease progressing to MIBC and becoming lethal, and as emphasised earlier patients who developed a NMIBC recurrence had similar OS and disease-specific survival (DSS) to those who did not.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

Not applicable.

Additional efficacy data needed in the context of a MA under exceptional circumstances

Not applicable.

3.3.7. Conclusions on clinical efficacy

The CHMP has identified multiple MO's, and a triggered GCP inspection is proposed. The credibility of the study conduct, validity of the database, and the clinical meaningfulness of the data are seriously questioned.

3.3.8. Clinical safety

There have been 3 clinical trials of intravesical VB4-845, Phase 1/2 (VB4-845-02-I), Phase 2 (VB4-845-02-IIA) and Phase 3 (VB4-845-02-IIIA) studies; all were open-label designs. Overall, from the 3 clinical studies, a total of 243 subjects have been exposed to the drug.

Patient exposure

Table 27: Study Subject Drug Exposure by Mean Daily Dose and Duration of Exposure

Duration (Weeks)	Total Dose (mg)							
	Phase 1/2 (VB4-845-02-I) (N=64)			Phase 2 (VB4-845-02-IIA) (N=46)		Phase 3 (VB4-845-02-III A) (N=133)	Total* (Any Dose)	Percent
	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	≥ 10.0 mg (N=33)	Treatment Schedule A, 30 mg (N=23)	Treatment Schedule B, 30 mg (N=23)	30 mg (N=133, all subjects received this dose)		
0 < Dur ≤ 1				30.0 (N=1)		30.0 (N=1)	N=2	0.8%
1 < Dur ≤ 2						120.0 (N=1)	N=1	0.4%
2 < Dur ≤ 4								
4 < Dur ≤ 12	0.60 N=4) 1.20 (N=3) 1.98 (N=5) 3.84 (N=5)	7.92 (N=3) 18.16 (N=5) 31.68 (N=6)	63.36 (N=5) 82.38 (N=3) 107.10 (N=7) 139.20 (N=10) 180.96 (N=8)	180.0 (N=4)	360.0 (N=12)	270.0 (N=1) 300.0 (N=2) 330.0 (N=1) 390.0 (N=1) 420.0 (N=3) 450.0 (N=1) 480.0 (N=4) 510.0 (N=8) 540.0 (N=42)	N=143	58.8%
12 < Dur ≤ 24				270.0 (N=10) 360.0 (N=2)	360.0 (N=2) 450.0 (N=2)	480.0 (N=1) 540.0 (N=1) 570.0 (N=2) 600.0 (N=1) 690.0 (N=1)	N=22	9.1%
24 < Dur ≤ 48				360.0 (N=3) 450.0 (N=3)	480.0 (N=1) 630.0 (N=2)	570.0 (N=1) 630.0 (N=1) 690.0 (N=2) 720.0 (N=4) 750.0 (N=5) 780.0 (N=3) 810.0 (N=2) 840.0 (N=2) 930.0 (N=5)	N=34	14.0%

Duration (Weeks)	Total Dose (mg)							
	Phase 1/2 (VB4-845-02-I) (N=64)			Phase 2 (VB4-845-02-IIA) (N=46)		Phase 3 (VB4-845-02-IIIA) (N=133)	Total* (Any Dose)	Percent
	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	≥ 10.0 mg (N=33)	Treatment Schedule A, 30 mg (N=23)	Treatment Schedule B, 30 mg (N=23)	30 mg (N=133, all subjects received this dose)		
48 < Dur ≤ 96					570.0 (N=1) 630.0 (N=3)	870.0 (N=1) 1020.0 (N=1) 1080.0 (N=1) 1110.0 (N=1) 1140.0 (N=1) 1230.0 (N=1) 1260.0 (N=3) 1350.0 (N=1) 1560.0 (N=1) 1650.0 (N=1)	N=16	6.6%

Duration (Weeks)	Total Dose (mg)							
	Phase 1/2 (VB4-845-02-I) (N=64)			Phase 2 (VB4-845-02-IIA) (N=46)		Phase 3 (VB4-845-02-IIIA) (N=133)	Total* (Any Dose)	Percent
	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	≥ 10.0 mg (N=33)	Treatment Schedule A, 30 mg (N=23)	Treatment Schedule B, 30 mg (N=23)	30 mg (N=133, all subjects received this dose)		
Dur > 96						1470.0 (N=1) 1530.0 (N=1) 1560.0 (N=1) 1590.0 (N=1) 1650.0 (N=1) 1680.0 (N=2) 1740.0 (N=2) 1770.0 (N=2) 1800.0 (N=5) 1830.0 (N=3) 1860.0 (N=3) 1890.0 (N=2)	N=24	9.9%
Mean (Any Duration)	37 days	37 days	37 days	108 days	163.0 days	255 days	N=243	100%
Percent of subjects[1]	26.6%	21.9%	51.6%	50.0%	50.0%	100.0%		

[1]This corresponds to the number of subjects in each dose group divided by the total number of subjects in the study.
* There were 177 patients who received multiple weekly doses of 30 mg in studies 2 and 3. A total of 132 of the 177 patients received the approved dose and schedule of 30 mg twice weekly for multiple weeks.
Intravesical Formulation, N= 243, Cutoff Date: October 06, 2020 (Phase 3 Study)
Data Source: Listing 16.2.5.1 (VB4-845-02-I); Listing 3.7.1 (VB4-845-02-IIA); Listing 16.2.5.1 (VB4-845-02-IIIA)

Adverse events

Table 28: Summary of Adverse Events

Category	All Subjects(n=133)
Any AE	123 (92%)
Grade 3-5 AEs	33 (25%)
Treatment-related AEs	73 (55%)
Treatment-related Grade 3-5 AEs	5 (4%)
Any SAE	21 (16%)
Treatment-related SAEs	3 (2%)
Discontinuations due to AEs	3 (2%)

Data Source: Table 14.3.1.1.1, Table 14.3.1.2.1, Table 14.3.1.4.1, Table 14.3.1.10 and Table 14.3.1.12

Table 29: Incidence of Adverse Events in Pooled Active Trial Database

	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	10.0 - < 30 mg (N=25)	30 mg OW 6 weeks (N=31)	30 mg OW 12 weeks (N=23)	30 mg BIW 6 weeks/ OW 6 weeks (N=133)	30 mg (N=187)	Total VB4-845 (N=243)
Number of Subjects with Any TEAE	14 (82%)	10 (71%)	15 (60%)	23 (74%)	22 (96%)	123 (92%)	168 (90%)	207 (85%)
Number of Subjects with Drug-related TEAE	9 (53%)	4 (29%)	5 (20%)	15 (48%)	17 (74%)	73 (55%)	105 (56%)	123 (51%)
Number of Subjects with Grade 3 or Higher TEAE	1 (6%)	1 (7%)	2 (8%)	4 (13%)	5 (22%)	33 (25%)	42 (22%)	46 (19%)
Number of Subjects with Any SAE	0	0	1 (4%)	0	4 (17%)	21 (16%)	25 (13%)	26 (11%)
Number of Subjects with Any Fatal SAE	0	0	1 (4%)	0	0	1 (< 1%)	1 (< 1%)	2 (< 1%)
Number of Subjects with Any TEAE Leading to Interruption of Study Drug	2 (12%)	0	2 (8%)	3 (10%)	3 (13%)	53 (40%)	59 (32%)	63 (26%)
Number of Subjects with Any TEAE Leading to Permanent Discontinuation from Study Drug	0	0	0	0	0	3 (2%)	3 (2%)	3 (1%)

Abbreviations: BIW=twice a week; OW=once a week; SAE=serious adverse event; TEAE=treatment emergent adverse event
Additional Information: Adverse events are coded using MedDRA V18.0 or higher preferred term and system organ classification. TEAEs are those starting after dosing. Only TEAEs with an onset date from the date of the first dose to 30 days post last dose are reported

Table 30: Incidence of Treatment-Emergent Adverse Events in Pooled Active Trial Database

System Organ Classification Preferred Term	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	10.0 - < 30 mg (N=25)	30 mg OW 6 weeks (N=31)	30 mg OW 12 weeks (N=23)	30 mg BIW 6 weeks/ OW 6 weeks (N=133)	30 mg (N=187)	Total VB4-845 (N=243)
Any TEAE	**14 (82%)**	**10 (71%)**	**15 (60%)**	**23 (74%)**	**22 (96%)**	**123 (92%)**	**168 (90%)**	**207 (85%)**
Renal and urinary disorders	**12 (71%)**	**4 (29%)**	**7 (28%)**	**21 (68%)**	**21 (91%)**	**91 (68%)**	**133 (71%)**	**156 (64%)**
Dysuria	4 (24%)	3 (21%)	5 (20%)	13 (42%)	17 (74%)	37 (28%)	67 (36%)	79 (33%)
Haematuria	2 (12%)	1 (7%)	1 (4%)	8 (26%)	4 (17%)	37 (28%)	49 (26%)	53 (22%)
Pollakiuria	5 (29%)	0	3 (12%)	4 (13%)	8 (35%)	22 (17%)	34 (18%)	42 (17%)
Micturition urgency	4 (24%)	0	3 (12%)	3 (10%)	7 (30%)	22 (17%)	32 (17%)	39 (16%)
Urinary incontinence	3 (18%)	0	1 (4%)	1 (3%)	3 (13%)	10 (8%)	14 (7%)	18 (7%)
Nocturia	2 (12%)	1 (7%)	1 (4%)	2 (6%)	5 (22%)	4 (3%)	11 (6%)	15 (6%)
Bladder spasm	0	1 (7%)	1 (4%)	2 (6%)	1 (4%)	8 (6%)	11 (6%)	13 (5%)
Haemorrhage urinary tract	2 (12%)	0	2 (8%)	2 (6%)	1 (4%)	4 (3%)	7 (4%)	11 (5%)
Bladder pain	1 (6%)	0	0	3 (10%)	2 (9%)	0	5 (3%)	6 (2%)
Urinary retention	1 (6%)	0	0	1 (3%)	1 (4%)	3 (2%)	5 (3%)	6 (2%)
Urinary tract pain	0	0	0	0	0	6 (5%)	6 (3%)	6 (2%)
Acute kidney injury	0	0	0	0	0	3 (2%)	3 (2%)	3 (1%)
Urine flow decreased	0	0	0	0	0	3 (2%)	3 (2%)	3 (1%)
Bladder discomfort	0	0	0	1 (3%)	0	1 (< 1%)	2 (1%)	2 (< 1%)
Chromaturia	0	0	0	0	0	2 (2%)	2 (1%)	2 (< 1%)
Cystitis noninfective	0	0	0	0	0	2 (2%)	2 (1%)	2 (< 1%)
Incontinence	1 (6%)	0	0	1 (3%)	0	0	1 (< 1%)	2 (< 1%)
Leukocyturia	0	0	0	0	0	2 (2%)	2 (1%)	2 (< 1%)
Infections and infestations	**4 (24%)**	**4 (29%)**	**6 (24%)**	**4 (13%)**	**7 (30%)**	**68 (51%)**	**79 (42%)**	**93 (38%)**
Urinary tract infection	3 (18%)	4 (29%)	4 (16%)	2 (6%)	4 (17%)	46 (35%)	52 (28%)	63 (26%)
Nasopharyngitis	0	0	1 (4%)	2 (6%)	1 (4%)	13 (10%)	16 (9%)	17 (7%)
Upper respiratory tract infection	0	0	0	0	1 (4%)	10 (8%)	11 (6%)	11 (5%)
Sinusitis	0	0	0	0	1 (4%)	5 (4%)	6 (3%)	6 (2%)
General disorders and administration site conditions	**6 (35%)**	**3 (21%)**	**4 (16%)**	**13 (42%)**	**7 (30%)**	**48 (36%)**	**68 (36%)**	**81 (33%)**
Fatigue	5 (29%)	2 (14%)	1 (4%)	6 (19%)	5 (22%)	21 (16%)	32 (17%)	40 (16%)
Oedema peripheral	0	0	0	0	3 (13%)	15 (11%)	18 (10%)	18 (7%)
Pyrexia	1 (6%)	0	2 (8%)	3 (10%)	2 (9%)	9 (7%)	14 (7%)	17 (7%)
Chills	1 (6%)	1 (7%)	1 (4%)	0	1 (4%)	4 (3%)	5 (3%)	8 (3%)
Influenza like illness	1 (6%)	0	0	4 13%)	1 (4%)	1 (< 1%)	6 (3%)	7 (3%)
Pain	0	0	0	1 (3%)	0	3 (2%)	4 (2%)	4 (2%)
Asthenia	0	0	0	1 (3%)	1 (4%)	1 (< 1%)	3 (2%)	3 (1%)
Non-cardiac chest pain	0	0	0	0	0	3 (2%)	3 (2%)	3 (1%)
Peripheral swelling	0	0	0	1 (3%)	0	2 (2%)	3 (2%)	3 (1%)
Catheter site related reaction	1 (6%)	0	0	1 (3%)	0	0	1 (< 1%)	2 (< 1%)
Device difficult to use	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Device leakage	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)

Gastrointestinal disorders	**4 (24%)**	**1 (7%)**	**2 (8%)**	**8 (26%)**	**5 (22%)**	**45 (34%)**	**58 (31%)**	**65 (27%)**
Diarrhoea	0	1 (7%)	1 (4%)	1 (3%)	2 (9%)	17 (13%)	20 (11%)	22 (9%)
Nausea	1 (6%)	1 (7%)	0	1 (3%)	1 (4%)	16 (12%)	18 (10%)	20 (8%)
Constipation	1 (6%)	0	1 (4%)	2 (6%)	0	11 (8%)	13 (7%)	15 (6%)
Vomiting	0	1 (7%)	0	1 (3%)	2 (9%)	7 (5%)	10 (5%)	11 (5%)
Abdominal pain	2 (12%)	0	0	0	0	7 (5%)	7 (4%)	9 (4%)
Dry mouth	1 (6%)	0	0	2 (6%)	0	2 (2%)	4 (2%)	5 (2%)
Musculoskeletal and connective tissue disorders	**7 (41%)**	**3 (21%)**	**3 (12%)**	**10 (32%)**	**6 (26%)**	**30 (23%)**	**46 (25%)**	**59 (24%)**
Arthralgia	2 (12%)	0	1 (4%)	1 (3%)	4 (17%)	9 (7%)	14 (7%)	17 (7%)
Back pain	2 (12%)	1 (7%)	0	1 (3%)	1 (4%)	7 (5%)	9 (5%)	12 (5%)
Pain in extremity	1 (6%)	0	0	2 (6%)	0	5 (4%)	7 (4%)	8 (3%)
Muscle spasms	1 (6%)	1 (7%)	0	1 (3%)	0	3 (2%)	4 (2%)	6 (2%)
Myalgia	1 (6%)	1 (7%)	1 (4%)	0	1 (4%)	1 (< 1%)	2 (1%)	5 (2%)
Flank pain	0	0	0	1 (3%)	0	3 (2%)	4 (2%)	4 (2%)
Joint swelling	0	0	0	1 (3%)	0	3 (2%)	4 (2%)	4 (2%)
Arthritis	0	0	0	1 (3%)	1 (4%)	0	2 (1%)	2 (< 1%)
Musculoskeletal chest pain	0	0	0	0	0	2 (2%)	2 (1%)	2 (< 1%)
Musculoskeletal discomfort	0	1 (7%)	0	1 (3%)	0	0	1 (< 1%)	2 (< 1%)
Neck pain	1 (6%)	0	0	0	0	1 (< 1%)	1 (< 1%)	2 (< 1%)
Bursitis	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Facial asymmetry	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Groin pain	0	0	0	1 (3%)	0	0	1 (< 1%)	1 (< 1%)
Investigations	**4 (24%)**	**2 (14%)**	**6 (24%)**	**3 (10%)**	**6 (26%)**	**35 (26%)**	**44 (24%)**	**56 (23%)**
Blood urine present	3 (18%)	1 (7%)	5 (20%)	1 (3%)	3 (13%)	1 (< 1%)	5 (3%)	14 (6%)
Nervous system disorders	**5 (29%)**	**3 (21%)**	**3 (12%)**	**6 (19%)**	**3 (13%)**	**24 (18%)**	**33 (18%)**	**44 (18%)**
Dizziness	3 (18%)	1 (7%)	1 (4%)	4 (13%)	2 (9%)	6 (5%)	12 (6%)	17 (7%)
Headache	1 (6%)	2 (14%)	0	0	0	8 (6%)	8 (4%)	11 (5%)
Amnesia	0	0	0	1 (3%)	0	3 (2%)	4 (2%)	4 (2%)
Diabetic neuropathy	1 (6%)	0	0	0	0	1 (< 1%)	1 (< 1%)	2 (< 1%)
Hypoaesthesia	0	0	1 (4%)	0	0	1 (< 1%)	1 (< 1%)	2 (< 1%)
Lethargy	0	0	2 (8%)	0	0	0	0	2 (< 1%)
Respiratory, thoracic and mediastinal disorders	**3 (18%)**	**2 (14%)**	**1 (4%)**	**2 (6%)**	**4 (17%)**	**22 (17%)**	**28 (15%)**	**34 (14%)**
Cough	2 (12%)	2 (14%)	0	0	1 (4%)	10 (8%)	11 (6%)	15 (6%)
Dyspnoea	1 (6%)	0	0	1 (3%)	1 (4%)	4 (3%)	6 (3%)	7 (3%)
Oropharyngeal pain	2 (12%)	1 (7%)	1 (4%)	0	0	3 (2%)	3 (2%)	7 (3%)
Nasal congestion	0	1 (7%)	0	1 (3%)	0	2 (2%)	3 (2%)	4 (2%)
Pulmonary mass	0	0	0	0	0	2 (2%)	2 (1%)	2 (< 1%)
Respiratory tract congestion	1 (6%)	1 (7%)	0	0	0	0	0	2 (< 1%)

AESI

Local Tolerance

Eighty-one (33%) subjects reported TEAEs based on the SOC of general disorders and administration site conditions. 3 (1%) subjects had TEAEs of Grade 3 severity and none reported events of Grade 4-5 severity. Forty (16%) reported fatigue, 18 (7%) reported peripheral oedema with 1 subject having Grade 3 severity. Pyrexia was reported in 17 (7%) of subjects, 3% subjects each reported chills (8 subjects) and influenza like illness (7 subjects), 4 (2%) subjects reported pain, 3 (1%) subjects each reported asthenia, non-cardiac chest pain and peripheral swelling. Two (<1%) subjects reported

catheter site related reaction and 1 (<1%) subject each reported TEAEs of device difficult to use, device leakage, discomfort, feeling cold, feeling hot, granuloma, infusion site pain, malaise, medical device complication, oedema, secretion discharge and suprapubic pain.

Development of Neoplasms

Six (2%) subjects reported TEAEs based on the SOC of neoplasms benign, malignant, and unspecified (including cysts and polyps). Four (2%) subjects had TEAEs of Grade 1-2 severity and only 1 (<1%) subjects reported a TEAE of Grade 4 severity that consisted of malignant lung neoplasm. Two (<1%) subjects each reported TEAEs of squamous cell carcinoma and squamous cell carcinoma of skin and 1 (<1%) subject each reported TEAEs of basal cell carcinoma and skin papilloma.

Serious adverse events and deaths

SAE

Table 31: Serious Treatment-Emergent Adverse Events in Pooled Active Trial Database

System Organ Classification Preferred Term	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	10.0 - < 30 mg (N=25)	30 mg OW 6 weeks (N=31)	30 mg OW 12 weeks (N=23)	30 mg BIW 6 weeks/ OW 6 weeks (N=133)	30 mg (N=187)	Total VB4-845 (N=243)
Any Serious TEAE	**0**	**0**	**1 (4%)**	**0**	**4 (17%)**	**21 (16%)**	**25 (13%)**	**26 (11%)**
Renal and urinary disorders	0	0	0	0	1 (4%)	8 (6%)	9 (5%)	9 (4%)
Acute kidney injury	0	0	0	0	0	3 (2%)	3 (2%)	3 (1%)
Haematuria	0	0	0	0	0	3 (2%)	2 (1%)	3 (1%)
Extravasation of urine	0	0	0	0	1 (4%)	0	1 (< 1%)	1 (< 1%)
Renal failure	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Urinary retention	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Cardiac disorders	0	0	1 (4%)	0	0	3 (2%)	3 (2%)	4 (2%)
Aortic valve disease	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Cardiac failure	0	0	1 (4%)	0	0	0	0	1 (< 1%)
Pericardial effusion	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Tachycardia	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Gastrointestinal disorders	0	0	0	0	0	4 (3%)	4 (2%)	4 (2%)
Small intestinal obstruction	0	0	0	0	0	3 (2%)	3 (2%)	3 (1%)
Oesophageal obstruction	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Infections and infestations	0	0	0	0	0	4 (3%)	4 (2%)	4 (2%)
Urinary tract infection	0	0	0	0	0	2 (2%)	2 (1%)	2 (< 1%)
Cystitis	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Pyelonephritis	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)

System Organ Classification Preferred Term	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	10.0 - < 30 mg (N=25)	30 mg OW 6 weeks (N=31)	30 mg OW 12 weeks (N=23)	30 mg BIW 6 weeks/ OW 6 weeks (N=133)	30 mg (N=187)	Total VB4-845 (N=243)
Injury, poisoning and procedural complications	0	0	0	0	1 (4%)	2 (2%)	3 (2%)	3 (1%)
Fall	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Hip fracture	0	0	0	0	1 (4%)	0	1 (< 1%)	1 (< 1%)
Rib fracture	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Vascular disorders	0	0	0	0	2 (9%)	0	2 (1%)	2 (< 1%)
Deep vein thrombosis	0	0	0	0	1 (4%)	0	1 (< 1%)	1 (< 1%)
Hypotension	0	0	0	0	1 (4%)	0	1 (< 1%)	1 (< 1%)
General disorders and administration site conditions	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Pyrexia	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Hepatobiliary disorders	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Hepatitis cholestatic	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Lung neoplasm malignant	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Nervous system disorders	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Cerebrovascular accident	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Reproductive system and breast disorders	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)
Pelvic pain	0	0	0	0	0	1 (< 1%)	1 (< 1%)	1 (< 1%)

Deaths

In total 3 patients died across all studies. The applicant has presented brief case narratives. None of the cases seem related to the oportuzumab. However, one of the cases that was due to renal failure, was originally assessed as related to treatment by the investigator. The applicant is asked to discuss this case.

Laboratory findings

Clinical chemistry

Table 32: Treatment-Emergent Laboratory Toxicities (Select Parameters)

Laboratory Panel Laboratory Parameter Severity	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	10.0 - < 30 mg (N=25)	30 mg OW 6 weeks (N=31)	30 mg OW 12 weeks (N=23)	30 mg BIW 6 weeks/ OW 6 weeks (N=133)	30 mg (N=187)	Total VB4-845 (N=243)
Any Treatment-Emergent Laboratory Toxicity	**15 (88%)**	**13 (93%)**	**19 (76%)**	**27 (87%)**	**23 (100%)**	**129 (97%)**	**179 (96%)**	**226 (93%)**
Grade 1	12 (71%)	11 (79%)	14 (56%)	19 (61%)	13 (57%)	49 (37%)	81 (43%)	118 (49%)
Grade 2	1 (6%)	2 (14%)	3 (12%)	6 (19%)	7 (30%)	50 (38%)	63 (34%)	69 (28%)

Laboratory Panel Laboratory Parameter Severity	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	10.0 - < 30 mg (N=25)	30 mg OW 6 weeks (N=31)	30 mg OW 12 weeks (N=23)	30 mg BIW 6 weeks/ OW 6 weeks (N=133)	30 mg (N=187)	Total VB4-845 (N=243)
Grade 3	1 (6%)	0	2 (8%)	2 (6%)	2 (9%)	24 (18%)	28 (15%)	31 (13%)
Grade 4	1 (6%)	0	0	0	1 (4%)	6 (5%)	7 (4%)	8 (3%)
Chemistry	**14 (82%)**	**13 (93%)**	**19 (76%)**	**27 (87%)**	**22 (96%)**	**127 (95%)**	**176 (94%)**	**222 (91%)**
Alanine Amino-transferase (IU/L)	**1 (6%)**	**0**	**1 (4%)**	**3 (10%)**	**3 (13%)**	**19 (14%)**	**25 (13%)**	**27 (11%)**
Grade 1	1 (6%)	0	1 (4%)	2 (6%)	3 (13%)	15 (11%)	20 (11%)	22 (9%)
Grade 2	0	0	0	1 (3%)	0	1 (<1%)	2 (1%)	2 (<1%)
Grade 3	0	0	0	0	0	3 (2%)	3 (2%)	3 (1%)
Grade 4	0	0	0	0	0	0	0	0
Albumin (g/L)	**2 (12%)**	**1 (7%)**	**0**	**1 (3%)**	**4 (17%)**	**14 (11%)**	**19 (10%)**	**22 (9%)**
Grade 1	2 (12%)	1 (7%)	0	1 (3%)	4 (17%)	11 (8%)	16 (9%)	19 (8%)
Grade 2	0	0	0	0	0	2 (2%)	2 (1%)	2 (<1%)
Grade 3	0	0	0	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Grade 4	0	0	0	0	0	0	0	0
Alkaline Phosphatase (IU/L)	**1 (6%)**	**0**	**0**	**1 (3%)**	**1 (4%)**	**17 (13%)**	**19 (10%)**	**20 (8%)**
Grade 1	1 (6%)	0	0	1 (3%)	1 (4%)	16 (12%)	18 (10%)	19 (8%)
Grade 2	0	0	0	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Grade 3	0	0	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0	0	0
Aspartate Amino-transferase (IU/L)	**0**	**3 (21%)**	**1 (4%)**	**2 (6%)**	**4 (17%)**	**19 (14%)**	**25 (13%)**	**29 (12%)**
Grade 1	0	3 (21%)	1 (4%)	2 (6%)	4 (17%)	16 (12%)	22 (12%)	26 (11%)
Grade 2	0	0	0	0	0	2 (2%)	2 (1%)	2 (<1%)
Grade 3	0	0	0	0	0	0	0	0

Laboratory Panel Laboratory Parameter Severity	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	10.0 - < 30 mg (N=25)	30 mg OW 6 weeks (N=31)	30 mg OW 12 weeks (N=23)	30 mg BIW 6 weeks/ OW 6 weeks (N=133)	30 mg (N=187)	Total VB4-845 (N=243)
Grade 4	0	0	0	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Bilirubin (mg/dL)	**0**	**0**	**1 (4%)**	**2 (6%)**	**2 (9%)**	**13 (10%)**	**17 (9%)**	**18 (7%)**
Grade 1	0	0	1 (4%)	2 (6%)	2 (9%)	10 (8%)	14 (7%)	15 (6%)
Grade 2	0	0	0	0	0	2 (2%)	2 (1%)	2 (<1%)
Grade 3	0	0	0	0	0	1 (<1%)	1 (<1%)	1 (<1%)
Grade 4	0	0	0	0	0	0	0	0
Creatinine (mg/dL)	**12 (71%)**	**10 (71%)**	**17 (68%)**	**22 (71%)**	**17 (74%)**	**111 (83%)**	**150 (80%)**	**189 (78%)**
Grade 1	10 (59%)	10 (71%)	17 (68%)	21 (68%)	16 (70%)	100 (75%)	137 (73%)	174 (72%)
Grade 2	2 (12%)	0	0	1 (3%)	1 (4%)	8 (6%)	10 (5%)	12 (5%)
Grade 3	0	0	0	0	0	2 (2%)	2 (1%)	2 (<1%)
Grade 4	0	0	0	0	0	1 (<1%)	1 (<1%)	1 (<1%)

Abbreviations: BIW=twice a week; OW=once a week

Note: Laboratory abnormalities are graded according to the NCI CTCAE v.4.03. Only treatment-emergent laboratory abnormalities with a collection date on or after the date of the first dose of study drug to 30 days post end of treatment and an increase of at least 1 grade from the baseline toxicity value are presented. For patients who experienced the laboratory abnormalities more than once, a single occurrence is presented and classified by highest toxicity grade.

Clinical haematology

The applicant has not provided an overview of clinical haematology in tabulated form. Instead reference is given to table 14.3.4.3, which consists of multiple pages, providing no overview. As for clinical chemistry (Table 42 in the Summary Clinical Safety), the applicant is asked to provide a similar table and discuss the results. Also, time to onset of Grade 3-4 AEs should be clarified, and it should be discussed whether these AEs resolved or not, and whether they resolved with or without sequelae. Finally, brief case narratives for patients with Grade 4 AEs should be presented and discussed.

Urinalysis

Time to onset of Grade 3-4 AEs should be clarified, and it should be discussed whether these AEs resolved or not, and whether they resolved with or without sequelae. Finally, brief case narratives for patients with Grade 4 AEs should be presented and discussed.

Vital signs

Table 33: Potentially Clinically Significant Vital Signs by Treatment Group: Safety Population

VITAL SIGN ASSESSMENT Clinically Significant Criteria	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	10.0 - < 30 mg (N=25)	30 mg OW 6 weeks (N=31)	30 mg OW 12 weeks (N=23)	30 mg BIW 6 weeks/ OW 6 weeks (N=133)	30 mg (N=187)	Total VB4-845 (N=243)
Diastolic Blood Pressure (mmHg)								
Any Potentially Clinically Significant Value	11 (65%)	7 (50%)	9 (36%)	14 (45%)	16 (70%)	106 (80%)	136 (73%)	163 (67%)
≤55 mmHg and/or a decrease of ≥20 mmHg from baseline	5 (29%)	1 (7%)	2 (8%)	8 (26%)	10 (43%)	59 (44%)	77 (41%)	85 (35%)
≥90 mmHg and/or an increase of ≥30 mmHg from baseline	7 (41%)	6 (43%)	7 (28%)	11 (35%)	10 (43%)	80 (60%)	101 (54%)	121 (50%)
Systolic Blood Pressure (mmHg)								
Any Potentially Clinically Significant Value	8 (47%)	1 (7%)	13 (52%)	12 (39%)	14 (61%)	89 (67%)	115 (61%)	137 (56%)
≤90 mmHg and/or a decrease of ≥30 mmHg from baseline	5 (29%)	1 (7%)	9 (36%)	8 (26%)	13 (57%)	50 (38%)	71 (38%)	86 (35%)
≥160 mmHg and/or an increase of ≥40 mmHg from baseline	4 (24%)	1 (7%)	9 (36%)	9 (29%)	8 (35%)	75 (56%)	92 (49%)	106 (44%)
Pulse Rate (beats/min)								
Any Potentially Clinically Significant Value	4 (24%)	0	1 (4%)	3 (10%)	3 (13%)	44 (33%)	50 (27%)	55 (23%)
≤50 bpm and/or a decrease of ≥30 bpm from baseline	3 (18%)	0	1 (4%)	2 (6%)	3 (13%)	34 (26%)	39 (21%)	43 (18%)
≥120 bpm and/or an increase of ≥30 bpm from baseline	2 (12%)	0	0	1 (3%)	0	18 (14%)	19 (10%)	21 (9%)
Temperature value > 38.3 °C	1 (6%)	0	0	0	0	0	0	1 (<1%)

Abbreviations: BIW=twice a week; bpm=beats per minute; OW=once a week

Note: Diastolic Blood Pressure values of ≤55 mmHg and/or a decrease of ≥20 mmHg from baseline or ≥90 mmHg and/or an increase of ≥30 mmHg from baseline are considered potentially clinically significant. Systolic Blood Pressure values of ≤90 mmHg and/or a decrease of ≥30 mmHg from baseline or ≥160 mmHg and/or an increase of ≥40 mmHg from baseline are considered potentially clinically significant. Pulse values of ≤50 bpm and/or a decrease of ≥30 bpm from baseline or ≥120 bpm and/or an

increase of ≥30 bpm from baseline are considered potentially clinically significant. Temperature values of > 38.3 °C are considered potentially clinically significant.

ECG

Table 14: Potentially Clinically Significant ECGs in the Safety Population (N=243)

ECG ASSESSMENT Clinically Significant Criteria	0.1 - < 1.0 mg (N=17)	1.0 - < 10.0 mg (N=14)	10.0 - < 30 mg (N=25)	30 mg OW 6 weeks (N=31)	30 mg OW 12 weeks (N=23)	30 mg BIW 6 weeks/ OW 6 weeks (N=133)	30 mg (N=187)	Total VB4-845 (N=243)
QTcB (msec)								
Any Potentially Clinically Significant Values	NA	NA	NA	NA	NA	47 (35%)	47 (25%)	47 (19%)
> 500 msec	NA	NA	NA	NA	NA	7 (5%)	7 (4%)	7 (3%)
> 480 msec	NA	NA	NA	NA	NA	14 (11%)	14 (7%)	14 (6%)
> 470 msec (female)/ > 450 msec (male)	NA	NA	NA	NA	NA	37 (28%)	37 (20%)	37 (15%)
Change from baseline ≥30 msec	NA	NA	NA	NA	NA	32 (24%)	32 (17%)	32 (13%)
Change from baseline ≥60 msec	NA	NA	NA	NA	NA	12 (9%)	12 (6%)	12 (5%)
QTcF (msec)								
Any Potentially Clinically Significant Values	NA	NA	NA	NA	NA	34 (26%)	34 (18%)	34 (14%)
> 500 msec	NA	NA	NA	NA	NA	4 (3%)	4 (2%)	4 (2%)
> 480 msec	NA	NA	NA	NA	NA	10 (8%)	10 (5%)	10 (4%)
> 470 msec (female)/ > 450 msec (male)	NA	NA	NA	NA	NA	25 (19%)	25 (13%)	25 (10%)
Change from baseline ≥30 msec	NA	NA	NA	NA	NA	29 (22%)	29 (16%)	29 (12%)
Change from baseline ≥60 msec	NA	NA	NA	NA	NA	6 (5%)	6 (3%)	6 (2%)

Abbreviations: NA=not available

QTcF values are calculated as QTcF=QT/cuberoot(60/HR) and QTcB values are calculated as QTcB=QT/squareroot(60/HR), where the values of QT and HR as reported in the clinical database.

Table 35: Interpretation of Shifts from Baseline in ECG: Safety Population (N=243)

	POST-BASELINE INTERPRETATION		
Treatment Baseline Interpretation	**Normal**	**Abnormal, Not Clinically Significant**	**Abnormal, Clinically Significant**
Treatment: 0.1 - < 1.0 mg (N=17)			

	POST-BASELINE INTERPRETATION		
Treatment Baseline Interpretation	**Normal**	**Abnormal, Not Clinically Significant**	**Abnormal, Clinically Significant**
Normal	4 (24%)	0	0
Abnormal, Not Clinically Significant	5 (29%)	8 (47%)	0
Abnormal, Clinically Significant	0	0	0
Treatment: 1.0 - < 10.0 mg (N=14)			
Normal	4 (29%)	1 (7%)	0
Abnormal, Not Clinically Significant	2 (14%)	6 (43%)	0
Abnormal, Clinically Significant	0	0	0
Treatment: 10.0 - < 30 mg (N=25)			
Normal	8 (32%)	6 (24%)	0
Abnormal, Not Clinically Significant	1 (4%)	6 (24%)	0
Abnormal, Clinically Significant	0	0	0
Treatment: 30 mg OW 6 weeks (N=31)			
Normal	1 (3%)	1 (3%)	0
Abnormal, Not Clinically Significant	0	5 (16%)	0
Abnormal, Clinically Significant	0	0	0
Treatment: 30 mg OW 12 weeks (N=23)			
Normal	0	0	0
Abnormal, Not Clinically Significant	0	0	0
Abnormal, Clinically Significant	0	0	0
Treatment: 30 mg BIW 6 weeks/OW 6 weeks (N=133)			
Normal	1 (< 1%)	1 (< 1%)	0
Abnormal, Not Clinically Significant	0	3 (2%)	0
Abnormal, Clinically Significant	0	0	0
Treatment: 30 mg (N=187)			
Normal	2 (1%)	2 (1%)	0
Abnormal, Not Clinically Significant	0	8 (4%)	0
Abnormal, Clinically Significant	0	0	0
Treatment: Total VB4-845 (N=243)			
Normal	18 (7%)	9 (4%)	0
Abnormal, Not Clinically Significant	8 (3%)	28 (12%)	0
Abnormal, Clinically Significant	0	0	0

Abbreviations: BIW=twice a week; OW=once a week;

In terms of overall QTcF in study VB-845-02-IIIA, the mean change from baseline to Week 12 was 7 msec, with a minimum of -55 and a maximum of 89 msec. Nine subjects (7%) had a QTcF > 470 msec change from baseline to Week 12.

The mean change from baseline to End of Treatment was 2 msec, with a minimum of -145 and a maximum of 142 msec. Eleven subjects (8%) had a QTcF of > 470 msec change from baseline to post-treatment.

Four subjects had at least one QTcF > 500 msec during the study.

• Subject [redacted] had a baseline QTcF of 404.5 msec and a maximum QTcF of 514 msec (the average of three ECGs was 457.2 msec) at week 12, for a change of 110 msec.

• Subject [redacted] had a baseline QTcF of 456 msec and a maximum QTcF of 520.6 msec (the average of three ECGs was 513 msec) at week 12, for a change of 64.6 msec.

• Subject [redacted] had a baseline QTcF of 375.6 msec and a maximum QTcF of 508.7 msec (the average of three ECGs was 437.8 msec) at End of Treatment, for a change of 133.1 msec.

• Subject [redacted] had a baseline QTcF of 407.5 msec and a maximum QTcF of 549.5 msec at the post-treatment visit (only one reading obtained) for a change of 142 msec.

Safety in special populations

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Total AEs				
Serious AEs – Total				
- Fatal				
- Hospitalisation/prolong existing hospitalisation				
- Life-threatening				
- Disability/incapacity				
- Other (medically significant)				
AE leading to drop-out				
Psychiatric disorders				
Nervous system disorders				
Accidents and injuries				
Cardiac disorders				
Vascular disorders				
Cerebrovascular disorders				
Infections and infestations				
Anticholinergic syndrome				
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
<other AE appearing more frequently in older patients>				

The applicant is asked to complete the above table.

The applicant is also asked to provide a table of AEs, SAEs and Grade 3-4 AEs as function of intrinsic and extrinsic factors, e.g. age, sex, ethnicity, smoking status, alcohol consumption, prior BCG status occupational risk, region.

Immunological events

All post-treatment ADA samples were positive for neutralising antibodies. However, the applicant claims that this did not have an effect on efficacy nor safety. The applicant is asked to present data for time to positive ADA status and to discuss the systemic absorption of oportuzumab monatox.

Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction studies were conducted with VB4-845.

Discontinuation due to AES

The number of AEs leading to discontinuation is very low, which gives the impression that oportuzumab is a well-tolerated medicinal product. However, this is in stark contrast to the safety profile of the product as discussed so far. The applicant is asked to comment on this.

The applicant is also asked to provide a table in line with table 26 from the CSR (VB4-845-02-IIIA) that shows AEs leading to interruption of therapy and discuss the results.

Post marketing experience

VB4-845 has never been approved for marketing and has been submitted to the FDA and EMA for approval as a first in class biologic treatment. As a result, no post-marketing data with VB4-845 is currently available.

3.3.9. Discussion on clinical safety

The safety database is limited to 243 patients, of which only 179 (133+23+23) patients received the recommended dose of 30 mg. The total safety database is considered small and the applicant is asked to discuss and make a proposal how the safety profile of oportuzumab monatox can be further investigated post-approval.

The number of patients expected to receive oportuzumab in the long-term is also considered limited, with only 11 subjects receiving oportuzumab up to 24 months (i.e. the maximum treatment duration studied). It could be of interest to know the exposure to oportuzumab during the maintenance phase so the applicant should provide the median number and range of doses received for patients who continued the maintenance period in study VB4-845-IIIA. In addition, the applicant should provide a complete safety data assessment for patients who received treatment after the induction phase in Study VB4-845-02-IIIA.

Almost all patients (92%) in the pivotal study experienced AEs. The majority of **AEs** are related to renal and urinary system (dysuria, haematuria), infections/infestations and general disorders, such as fatigue. There seems to be a reverse dose-dependent AE profile. The number total AE seem to fall as the dose is increased from 0.1 mg to 30 mg. Although acknowledging that the numbers are small, the pattern is not understood. The applicant is asked to clarify.

Local tolerance and development of neoplasms were analysed as AEs of special interest, but it is unknown the reasons that led the applicant to select these events as AESI and this should be clarified.

Regarding secondary neoplasms, the number of events seems worrying considering the small size of this safety population. It is acknowledged that the nature of the reported neoplasms (skin squamous cell carcinoma, basal cell carcinoma and skin papilloma) is compatible with the advanced age of the included subjects (73.6 years) and the limited exposure to the study drug that has been reported for the overall population makes the plausibility of a relation between oportuzumab and the appearance of secondary neoplasms highly unlikely. It could however be of interest to know the individual exposure these subjects had to the study treatment.

Furthermore, oportuzumab seems to have an effect on the **cardio-vascular system** (changes in pulse and blood pressure) in a substantial number of patients. The applicant is asked to present post-baseline shifts in pulse, diastolic blood pressure and systolic blood pressure. The applicant is also asked to provide a table with Grade 3 and 4 (separated) AEs related to pulse, diastolic blood pressure, systolic blood pressure, bradycardia, tachycardia, syncope, and discuss the results.

In total, 26% (34/133) of the patients in the pivotal study had "any potentially clinically significant value" with regards to **QTcF**, 22% (29/133) had a change from baseline >=30 msec, while 5% (6/133) had a change from baseline >= 60 msec. The applicant claims that there were no reports of torsade de pointes, sudden death, ventricular fibrillation and flutter or seizures. It is intriguing that a locally administered product leads to a considerable number of AEs related to the cardiovascular system. Considering these findings and the potential systemic absorption that is suspected based on the reported safety data, further discussion about a possible increased risk of QT prolongation with oportuzumab should be provided by the applicant.

In total, 22% (30/133) of the patients in the pivotal study experienced **Grade 3-4 AEs**. Amongst these there were three cases Grade 3 ALT increase, one case of Grade 4 AST increase and one case of Grade 3 bilirubin increase. The applicant is asked to clarify, how many patients fulfilled Hy's law and whether there were any cases of DILI.

Also, 83% of the patients had increased creatinine levels. BCG is not associated with renal toxicity, however, oportuzumab monatox seems to pose significant renal toxicity. If these cases of creatine increase are due to dehydration, then the applicant should discuss how this is reflected in the number of cases of dehydration detected in the pivotal study.

Furthermore, oportuzumab has an extremely toxic payload, and the applicant is asked to discuss whether a reflux of oportuzumab monatox back to the kidney, where it potentially could be absorbed, indeed could be the reason for the unexpected findings with regards to systemic toxicity especially in terms of renal, cardiac and liver toxicity.

Oportuzumab is not expected to cause any relevant drug-drug interactions due to its apparent low systemic absorption. According to the phase III CSR, plasma samples were analysed for 113 of 133 subjects. Only one patient had oportuzumab detectable in plasma but, despite this fact, safety data suggest that there is a relation between oportuzumab systemic exposure and incidence of adverse events since there is a high percentage of events that are not expected from a medicinal product for vesical instillation. It is unknown if these effects might be caused by circulating drug that was not detected by the used assay or by the immunogenicity oportuzumab produces. If this is confirmed, then toxicity related to drug-drug interactions could not be excluded. The applicant should further elaborate on this.

Time to onset of **Grade 3-4 AEs** should be clarified, and it should be discussed whether these AEs resolved or not, and whether they resolved with or without sequelae

Overall, 16% of the patients in the pivotal study experienced **SAEs**. These were mainly related to renal and urinary disorders, and infections. The MAH is asked to provide brief case narratives from all 21 patients with SAEs from the pivotal study and discuss them. Time to onset SAE should be clarified, and it should be discussed whether these SAEs resolved or not, and whether they resolved with or without sequelae.

In total 3 patients **died** across all studies. The applicant has presented brief case narratives. None of the cases seem related to the oportuzumab.

The applicant has not in a satisfactory manner discussed safety as function of intrinsic and extrinsic factors, and has been asked to do so.

Although AEs incidences by SOC and PT have been submitted based on 75 years cut-off, a table with general data from overall TEAEs, related-TEAEs, Grade ≥ 3 AEs, SAEs, AESI and AEs leading to discontinuation should be provided for a better safety assessment in elderly. Number of patients included in both age groups should also be detailed.

All post-treatment ADA samples were positive for neutralising antibodies. However, the applicant claims that this did not have an effect on efficacy nor safety. The applicant is asked to present data for time to positive ADA status and to discuss the systemic absorption of oportuzumab monatox.

Systemic drug exposure is suspected, toxicity related to drug-drug interactions cannot be excluded. The applicant should further elaborate on this.

The number of AEs leading to discontinuation is very low, which gives the impression that oportuzumab is a well-tolerated medicinal product. However, this is in stark contrast to the safety profile of the product as discussed so far. The applicant is asked to comment on this.

Although oportuzumab has been associated with several adverse events, a limited number of them led to treatment permanent discontinuation, only three patients. The percentage of temporary treatment interruptions due to AEs is unknown which could give us an idea of the real tolerance of oportuzumab treatment. According to the study protocol, in subjects who developed low-grade papillary disease while on treatment, study drug should be interrupted for a minimum of 2 weeks following tumour removal. Also, criteria for holding oportuzumab treatment based on serum creatinine or creatinine clearance levels were defined in the protocol. It was recommended to hold oportuzumab for any subject whose AST or ALT doubles from their baseline value and is >2x ULN or bilirubin >2 mg/dL (>34 micromol/L), according to criteria included in this same version of the protocol. The same recommendation of holding treatment included UTI requiring antibiotics and any Grade 3 or greater toxicity. However, these interruptions are not reflected in the PI.

The basis for information included in Sections 4.4 and 4.8 of the SmPC is unclear. The applicant should justify all safety data included in the PI.

Additional expert consultation

Not foreseen for the time being.

Assessment of paediatric data on clinical safety

N/A

Additional safety data needed in the context of a MA

The applicant seeks a full approval, and has been asked to justify, how their dossier can be considered comprehensive.

3.3.10. Conclusions on clinical safety

Although most of the AEs reported were somehow expected for a medicinal product which is administered as a vesical instillation, there were some observed events (gastrointestinal AEs, hepatotoxicity and signs of nephrotoxicity) that led to a suspicion about a higher than expected systemic exposure to oportuzumab. In addition, most of these events were observed also in non-clinical studies, in which a systemic route was used therefore providing some support to the observations. The applicant should discuss this issue, including a possible explanation for the observed systemic adverse events and reasons why, even though almost none of the subject samples were positive to detectable drug serum levels, it appears that systemic exposure to oportuzumab may be greater than expected and also greater than claimed.

In conclusion, the assessment of safety is based on a limited database, with limited exposure. Long-term safety data are lacking. Concerns are raised with regard to the reliability of the safety database. The applicant claims that there is no substantial systemic absorption, but this is in stark contrast to the safety findings so far. This is based on the non-intuitive patterns in the safety data, the cardio-vascular, renal and liver safety profile, and the extent of neutralising antibodies.

A GCP inspection should be triggered to determine reliability of the database.

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant proposed the following summary of safety concerns in the RMP rev. 0.1 with data lock point 06 Oct. 2020:

Table 36: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

3.4.2. Discussion on safety specification

The applicant has not listed any safety concerns. This is not acceptable, especially when bearing in mind the observed safety profile, where concerns are raised about the cardiac, renal and liver toxicity and the fact that oportuzumab has one of the most toxic payloads. There are currently also concerns with regard to systemic absorption of oportuzumab monatox. This is based on systemic AE/ADR and the fact that all patients developed neutralising antibodies.

Almost all patients experienced AEs. A substantial number experienced AEs related to the cardiovascular system, e.g. QTc prolongation, increase in blood pressure, heart rate, etc. The concerns

about systemic absorption are further supported by a total of 22% (30/133) of patients experiencing Grade 3-4 AEs, amongst them signs of liver injury in terms of increase in ALT, AST and bilirubin.

Furthermore, long-term safety is lacking.

3.4.3. Conclusions on the safety specification

Having considered the data in the safety specification the CHMP considers that following should be safety concerns:

- Important identified risks:
    - Nephrotoxicity
    - Hepatotoxicity
- Important potential risks:
    - ADRs due to systemic exposure
    - Embryo-fetal toxicity
- Missing information:
    - Long-term safety

3.4.4. Pharmacovigilance plan

Routine pharmacovigilance activities are proposed by the applicant.

No additional pharmacovigilance activities have been proposed by the applicant.

No safety concerns were proposed by the applicant and, consequently, no specific PhV activities were proposed apart from general routine pharmacovigilance. Taking into account the CHMP Rapporteur's recommendations for safety concerns to be included in the safety specification, the applicant should propose a PhV plan to monitor and further characterise the proposed safety concerns. As a preliminary view, additional PhV activities are indicated at least for the proposed area of missing information of long-term safety; furthermore, the need for further characterisation through post-authorisation studies needs to be discussed for the remaining safety concerns. Thus, the need for additional PhV activities should be discussed for each of the safety concerns and a proposal for post-authorisation studies needs to be submitted.

The PRAC Rapporteur, having considered the data submitted, and the comments and recommendations by the CHMP Rapporteur, is of the opinion that the applicant should propose a post-authorisation PhV plan, including a proposal for additional PhV activities, to address the safety concerns recommended to be included in the safety specification.

3.4.5. Risk minimisation measures

No safety concerns were proposed by the applicant and, consequently, no risk minimisation measures are listed in this section of the RMP. Taking into account the CHMP Rapporteur's recommendation for safety concerns, the applicant should propose appropriate risk minimisation measures.

The PRAC Rapporteur having considered the data submitted, and the comments and recommendations by the CHMP Rapporteur, was of the opinion that risk minimisation measures should be proposed for the safety concerns recommended to be included in the safety specification.

3.4.6. Conclusion on the RMP

Based on the recommendation for safety concerns to be included in the RMP, appropriate pharmacovigilance activities and risk minimisation measures should be proposed to address these safety concerns.

The RMP Part III-VI could be acceptable provided an updated RMP and satisfactory responses to the list of questions (see section 6.4) is submitted.

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

N/A at present

4. Benefit risk assessment

4.1. Therapeutic Context

4.1.1. Disease or condition

The applicant is seeking a MA for the following *proposed indications*:

• the treatment and prevention of recurrence of carcinoma in situ (CIS) of the urinary bladder following transurethral resection in BCG-unresponsive patients.

• the prevention of recurrence of high-grade Ta and/or T1 papillary tumours following transurethral resection in BCG-unresponsive patients.

Bladder cancer is the seventh most commonly diagnosed cancer in the male population worldwide, while it drops to eleventh when both genders are considered (EAU). Bladder cancer is a general term for several types of malignant tumours of the urinary bladder. NMIBC, or superficial bladder cancer, accounts for approximately 75-85% of bladder cancer, and is either confined to the mucosa (Stage Ta, CIS) or submucosa (Stage T1). Approximately 70% of NMIBC cases present as stage Ta, 20% as T1 and 10% as CIS.

The aim of oportuzumab monatox treatment is to delay time to cystectomy in patients with non-muscle invasive bladder cancer who have failed prior treatment with BCG.

4.1.2. Available therapies and unmet medical need

The NCCN Guidelines for Bladder Cancer generally manage NMIBC with intravesical therapy or, for those at particularly high risk, cystectomy. The high recurrence and progression rates of NMIBC have led investigators to study the use of intravesical therapy in order to prevent them. Bacillus Calmette–Guérin (BCG) has been successfully used for this indication to treat NMIBC for more than four decades and is considered the golden standard when more aggressive therapy like cystectomy or in selected cases, bladder-sparing options like chemo-radiation, are not yet required.

For other intravesical possibilities phase III trials have reported a reduced risk of recurrence for patients with suspected NMIBC who are treated with immediate postoperative gemcitabine or

mitomycin. Another phase III, prospective, multicentre, randomised study of 2,844 patients with NMIBC showed that an immediate instillation of mitomycin C after TURBT reduces recurrence regardless of the number of adjuvant instillations. BCG has also been compared with gemcitabine and epirubicin. Pembrolizumab has also shown promising results in a phase II study and is now followed by a phase III study randomising +/- pembrolizumab in conjunction with BCG.

Taken the above-mentioned treatment possibilities in mind the applicant cannot claim an unmet medical need for the chosen study population. Instead the applicant should have chosen subjects not eligible or not willing to undergo RC. For those subjects there is a true unmet medical need.

4.1.3. Main clinical study

The VB4-845-02-IIIA study (N=133) was an open-label, non-randomised, multicentre, multiple-dose, study of oportuzumab in subjects with histologically-confirmed NMIBC in situ (CIS) and/or papillary disease (high grade Ta or any grade T1) of the bladder who failed previous treatment with BCG.

Three cohorts of subjects were enrolled:

• Cohort 1: Subjects with CIS with or without associated papillary disease whose disease was determined to be refractory or recurred within 6 months of the last dose of adequate BCG treatment (N=86).

• Cohort 2: Subjects with CIS with or without associated papillary disease whose disease was determined to have recurred more than 6 months but within 11 months of the last dose of adequate BCG treatment (N=7).

• Cohort 3: Subjects with high-grade Ta or any grade T1 papillary disease (without CIS) whose disease recurred within 6 months of the last dose of adequate BCG treatment (N=40).

The study consisted on a 2-year treatment period and a follow-up post-treatment period of up to 2 years. The treatment period included an induction phase of 12 weeks and a maintenance phase up to a total of 24 months (104 weeks). Oportuzumab monatox was administered intravesically at a dose of 30 mg. Data provided so far are based on a data cut-off date of 6 Oct 2020, when all patients had completed the treatment period.

4.2. Favourable effects

In the primary efficacy population (cohort 1+2) 39% (36/93) of subjects achieved a complete response at 3 months while the CR rate for the evaluable subjects at 3 months was 40% (36/89).

The Kaplan-Meier estimate for the median duration of response was 283 days (9.3 months).

Of the 36 mITT subjects that achieved a complete response at 3 months, the CR was sustained in 72% (26/36), 53% (19/36), 42% (15/36), 36% (13/36), 36% (13/36), 33% (12/36) and 31% (11/36) of those subjects at 6, 9, 12, 15, 18, 21, and 24 months, respectively.

In papillary patients (cohort 3), the recurrence-free rates were 68%, 55%, 43% and 30% at 3, 6, 12 and 24 months, respectively.

By Kaplan-Meier estimate 90.2% of all patients that were disease-free at 3 months were cystectomy-free beyond 2 years from the start of treatment compared with 60.6% of non-responders at 3 months.

4.3. Uncertainties and limitations about favourable effects

The selection of the 30 mg intravesical dose was based on data from a dose escalating Phase 1/2 study VB4-845-02-I, in which 12 dose levels were tested (from 0.1 mg to 30.16 mg) and no DLT was observed. While a lower rate of disease progression among patients receiving ≥10 mg (n=33) was observed, since four dose levels were included within this range (13.73, 17.85, 23.20 or 30.16 mg), the rationale to choose 30 mg is not clear and should be further justified.

The applicant has chosen to evaluate CR at different times using the total number of responders at 3 months in the denominator as a selected "subset" group and not all eligible (or all treated with at least one dose) subjects. The sustained CR (sCR) has not been controlled for multiplicity neither the study has been powered to this endpoint.

While the sCR seems stable, CR calculated using the mITT falls over time to a much larger extent, indicating that approximately 16% of patients who initiate this therapy will be responders at month 12. This is not in line with recently established complete response benchmarks where a clinically meaningful CR at 12 months is considered to be at least 30%.

The benefit of Oportuzumab monatox in patients with NMIBC is uncertain. With regards to the CIS population, while some activity has been observed, the duration of the effect appears limited, with only 11 patients remaining in response at the end of treatment period (i.e. 24 months). The efficacy in patients with papillary disease is difficult to interpret, due to the single-arm design of the study and therefore, no conclusions can be drawn.

The follow-up time of 30 months was too short (retrospective studies show that 24% of CRs developed a NMIBC recurrence after combined-modality therapy (CMT) after mean follow-up of 5.1 years [Sanchez A., 2018]).

The main limitation is the non-comparative design of the pivotal study hampering interpretation of time-to-event endpoints as well as the low number of patients enrolled. .

Statistical aspects as unclear censoring rules, which patients had an event, the reasons for censoring, the presented sample size is not relevant to the current study (the CR at 12 months was used for the sample size calculations when the primary endpoint was CR at 3 months) and it is unclear why the study is considered successful. Additionally, the sample size calculation does not seem taken into account study discontinuation, initiation of another therapy before progression, or RC.

The primary endpoint of CR at 12 months was changed to CR at 3 months while the study was ongoing.

It is not clear if a prior TURB was required for all patients before the first dose of study treatment and whether residual disease was present in all CIS patients after the TURB.

GCP compliance issues with uncertainties and concerns about credibility of data.

4.4. Unfavourable effects

- Almost all patients (92%) in the pivotal study experienced **AEs**. The majority of AEs are related to renal and urinary system (dysuria, haematuria), infections/infestations and general disorders, such as fatigue.
- In total, 26% (34/133) of the patients in the pivotal study had "any potentially clinically significant value" with regards to **QTcF**, 22% (29/133) had a change from baseline >=30 msec, while 5% (6/133) had a change from baseline >= 60 msec.

- In total, 22% (30/133) of the patients in the pivotal study experienced **Grade 3-4 AEs**. Amongst these there were three cases Grade 3 ALT increase, one case of Grade 4 AST increase and one case of Grade 3 bilirubin increase.
- Overall, 16% of the patients in the pivotal study experienced **SAEs**. These were mainly related to renal and urinary disorders, and infections.

4.5. Uncertainties and limitations about unfavourable effects

- Long-term safety is lacking.
- There seems to be a reverse dose-dependent AE profile. The number of the total AEs seem to fall as the dose is increased from 0.1 mg to 30 mg. Although acknowledging that the numbers are small, the pattern is not understood. The applicant is asked to clarify.
- All post-treatment ADA samples were positive for neutralising antibodies. However, the applicant claims that this did not have an effect on efficacy nor safety. The applicant is asked to present data for time to positive ADA status and to discuss the systemic absorption of oportuzumab monatox.
- Although most of the reported AEs were somehow related to the intravesical administration route and the intended local action of oportuzumab, there were some observed AEs that could suggest a higher systemic exposure than expected (i.e. renal failure, gastrointestinal disorders, elevated liver enzymes…). Some of these adverse events have also been reported in non-clinical trials. This fact is of concern, taking into account the small safety dataset and limited treatment exposure.
- The applicant has not discussed safety as function of intrinsic and extrinsic factors in a satisfactory manner, and has been asked to do so.
- Also, 83% of the patients had increased creatinine levels. BCG is not associated with renal toxicity, however, oportuzumab monatox seems to pose significant renal toxicity. If these cases of creatine increase are due to dehydration, then the applicant should discuss, how this is reflected in the number of cases of dehydration detected in the pivotal study.
- Furthermore, oportuzumab monatox has an extremely toxic payload, and the applicant is asked to discuss whether a reflux of oportuzumab monatox back to the kidney, where it potentially could be absorbed, indeed could be the reason for the unexpected findings with regard to systemic toxicity especially in terms of renal, cardiac and liver toxicity.

  Local tolerance and development of neoplasms were selected as AESI but the reasons that led to that choice are unclear.

4.6. Effects Table

Table 37. Effects Table for oportuzumab (data cut-off:06 Oct 2020).

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Endpoints			Oportuzumab Cohort 1+2 N=93	NA	Uncontrolled study design, unclear sample size calculation, unclear when study is successful	
			Oportuzumab Cohort 3 N=40	NA		
Primary endpoint	Complete Response (CR) at 3,6,9,12,15, 18,21,24 months	39,28,20, 16,14,14, 14,14%	Oportuzumab Cohort 1+2 N=93	NA		
Secondary endpoint	Recurrence free survival (RFS) at 3,6,9,12,15, 18,21,24 months	68,55,43, 43,33,33, 33,30%	Oportuzumab Cohort 3 N=40	NA		
Exploratory endpoint	Sustained Complete Response (sCR) at 3,6,9,12,15, 18,21,24 months	72,53,42, 36,36,33, 31%	Oportuzumab Cohort 1+2 N=36 (number of subjects with CR at 3 months)	NA		
Unfavourable Effects						
Creatine increase		%	83% (111/133)*			
ALT increase		%	14% (19/133)*			
AST increase		%	14% (19/133)*			
Bilirubin increase		%	10% (13/133)*			
Creatine increase		%	83% (110/183)			
QTcF		%	26% (34/133)*			
Grade 3-4 AEs		%	22% (30/133)*			
SAE		%	16% (21/133)*			

Notes: * = the pivotal study

4.7. Benefit-risk assessment and discussion

4.7.1. Importance of favourable and unfavourable effects

The applicant submitted data on one pivotal study VB4-845-02-IIIA, an open-label, non-randomised, multicentre study in subjects with BCG-unresponsive Non-Muscle-Invasive bladder cancer (NMIBC) designed to establish the efficacy and safety of oportuzumab administered as an intravesical instillation. The applicant did not follow the advice given by CHMP in 2009 to "*proceed to the randomised controlled trial based on the phase II results available and not to divert patients into an uncontrolled trial that is likely to be at most only supportive".*

The target population studied is BCG-unresponsive subjects with CIS with and without associated papillary disease and high-grade Ta and/or T1 papillary tumours alone following TURB which is considered relevant. It is though not clear if a prior TURB was required for all patients before the first dose of study treatment and whether residual disease was present in all CIS patients after the TURB. However, the wording of the indication is not reflective of the study design, since evidence for preventing development of disease requires not only lack of disease at baseline but also interpretation of time-dependent endpoints which is not possible in the absence of a comparator. With this in mind it is not possible to isolate the treatment effect of oportuzumab monatox in preventing recurrence of high grade Ta and/or T1 papillary tumours (i.e. the second part of the indication). Additionally, as mentioned, the pivotal study is a 'treatment' study where histologically proven CIS is present in all subjects in cohort 1+2 at baseline, rather than a prophylaxis study where disease would need to have been previously resected. An indication for the prevention of recurrence of CIS is therefore not supported.

In preventing or postponing radical cystectomy as the only curative opportunity the applicant claims an unmet medical need for the chosen study population as there are no effective pharmacologic comparator available and the majority of BCG-unresponsive patients will refuse RC. The applicant's arguments are challenged since there are other treatment possibilities and since the effectiveness of oportuzumab is not yet established without a randomised trial it is considered ethical to randomise the patients. BCG-unresponsive patients refusing RC could be avoided by enrolling solely patients not eligible for or unwilling to undergo RC. The rationale for not implementing a randomised controlled trial as originally planned by the applicant (Trial B) is not understood.

Without a comparator it has to be justified that the proposed endpoint is able to isolate treatment effect. Furthermore, (clinical) interpretation of time-to-event endpoints is hampered by the study design. In addition, the expected effect size or efficacy hypothesis of the study was not mentioned in the protocol. It was neither described which was the response criterium required to consider the study successful. The sample size calculation is unclear since the original CR at 12 months was used and hence not relevant for the study. Furthermore, the applicant has changed the primary endpoint from CR at month 12, to CR without time and DoR to CR at month 3 and DoR. However, the primary endpoint at 3 months is not considered informative.

With regards to safety, the assessment of safety is based on a limited database, with limited exposure. Long-term safety data are lacking. Concerns are raised with regard to the reliability of the safety database. The applicant claims that there is no substantial systemic absorption, but this is in stark contrast to the safety findings so far. This is based on the cardiovascular, renal and liver safety profile, and the extent of neutralising antibodies.

A GCP inspection should be triggered to determine the reliability of the database.

4.7.2. Balance of benefits and risks

The B/R balance is currently negative due to several MOs.

4.7.3. Additional considerations on the benefit-risk balance

Not applicable

Conditional marketing authorisation

Not applicable

Marketing authorisation under exceptional circumstances

Not applicable

4.8. Conclusions

The overall B/R of Oportuzumab monatox DLRC Pharma Services is negative.

5. Biosimilarity assessment

Not applicable.