

MYCOBACTERIUM PHLEI CELL WALL-NUCLEIC ACID COMPLEX  
(MCNA) FOR THE TREATMENT OF  
NON-MUSCLE-INVASIVE BLADDER CANCER

BRIEFING DOCUMENT FOR THE JOINT MEETING OF  
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## LIST OF ABBREVIATIONS USED IN TEXT

<b>Abbreviation</b>	<b>Definition</b>
AUA	American Urological Association
BCG	bacillus Calmette-Guérin
BLA	Biological License Application
CIS	carcinoma <i>in situ</i>
DNA	deoxyribonucleic acid
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
IL	interleukin
ITT	intent-to-treat
IND	Investigational New Drug
MCC	Mycobacterial Cell Wall-DNA Complex
MCNA	Mycobacterium phlei Cell Wall-Nucleic Acid Complex
MCWE	Mycobacterial Cell Wall Extract
mITT	modified intent-to-treat
NMIBC	non-muscle-invasive bladder cancer
PUNLMP	papillary urothelial neoplasm of low malignant potential
WHO	World Health Organization

Note: Abbreviations used only in a table or figure are defined with the table or figure.

## EXECUTIVE OVERVIEW

Telesta Therapeutics Inc. (Telesta) is seeking approval of Mycobacterium phlei Cell Wall-Nucleic Acid Complex (MCNA) for intravesical use in the treatment of non-muscle-invasive bladder cancer (NMIBC) at high risk of recurrence or progression in adult patients who failed prior bacillus Calmette-Guérin (BCG) immunotherapy, e.g., in patients who are BCG refractory or BCG relapsing. MCNA is a novel, microbiologically-derived, antineoplastic agent with immune-stimulant and direct anti-cancer activity.

Bladder cancer is the most common malignant tumor in the urinary tract, accounting for over 4.5% of all new cases of cancer in the United States. NMIBC accounts for about 75% of bladder cancer cases, and of these, half are high grade disease. A top treatment priority is to prevent high grade NMIBC from becoming muscle-invasive and/or metastatic disease, which has a poor survival prognosis. Unfortunately, the treatment paradigm for high risk NMIBC has been essentially unchanged since the last drug approval by the United States Food and Drug Administration (FDA) in 1998.

For BCG failures, current treatment guidelines recommend radical cystectomy, i.e., bladder removal. Radical cystectomy is a complex surgery, requiring 6 to 8 hours under anesthesia, 5 to 10 days in the hospital, and a 6- to 8-week recovery period. The procedure is associated with at least 28% to 45% surgical complications and 2% to 3% mortality, with up to 8% mortality within 6 months of surgery in the elderly population. The life-altering surgery also negatively impacts multiple aspects of quality of life, with consequences including urinary incontinence, ostomy, loss of sexual function, low self-esteem, and reduced social interaction. Patients who refuse or who do not qualify for bladder removal face an increased risk of progression to muscle-invasive disease, likely leading to metastases and death. MCNA offers a new treatment option for these patients.

Telesta's Study 301, which provides the primary evidence for the efficacy and safety of MCNA, was an open-label, single-arm, multicenter study. The study was divided into 3 phases (Induction, Maintenance, and Follow-Up). The Induction Phase consisted of the first 6 weeks of the study, the Maintenance Phase lasted from Month 3 to Month 24, and the Follow-Up Phase lasted from Month 24 up to Month 60. The primary efficacy endpoint of the study was disease-free survival at 1 year (as a percentage).

### Clinical Efficacy

Approximately 24% of the treated patients were disease-free at 1 year. Among patients who were disease-free at this time point, the response to MCNA was durable and lasted almost 3 years. In addition, patients treated with MCNA were not placed at greater risk of progression, bladder removal, or death; most importantly, patients were provided a potentially bladder-preserving treatment without undue risk from a delay in surgery.

Evidence for these conclusions includes:

- Among all 28 responders at 1 year, the median duration of response was 34.0 months.
- Progression-free survival at 1 year was 85.0% among all treated patients; this is consistent with historical reports for high risk NMIBC.

- For responders at Month 6, the progression-free survival rate was 85.7% at 3 years. For non-responders at Month 6, the progression-free survival rate was 74.2% at 3 years. Note that this analysis excludes patients who discontinued the study or experienced progression before Month 6.
- The bladder was preserved for most patients.
  - A total of 55 out of 129 patients underwent bladder removal over the study period, with a median time to bladder removal of 263 days from the first instillation of MCNA. Among patients for whom MCNA failed, median time from MCNA treatment failure to bladder removal was 173.5 days.
  - The rate of bladder removal among patients who responded to MCNA at 1 year was 17.9% (5 out of 28 patients), compared to 49.5% (50 out of 101 patients) among patients who did not respond to MCNA at 1 year.
  - Among the 55 patients, 17 had muscle-invasive or metastatic disease at time of bladder removal.
  - Within the 55 patients who underwent cystectomy, 13 (24%) received additional intravesical therapy between MCNA failure and the subsequent cystectomy, compared to the non-cystectomy group in which 34 (46%) of 74 patients received intravesical therapy after MCNA failure.
- Results for subpopulations based on specific baseline characteristics include:
  - Among all treated patients with carcinoma *in situ* (CIS) with or without papillary tumors, the complete response rate at 1 year was 18.7%. The complete response rate was 15.1% and 33.3% for the BCG refractory and BCG relapsing populations, respectively. Among the 17 responders with CIS, the median duration of response was 26.0 months.
  - Among all treated patients with papillary tumors only, the disease-free survival rate at 1 year was 33.6%. Among the 11 responders with papillary tumors only who were disease free at 1 year, the median duration of response was 38.8 months.

## Safety

A total of 166 patients received at least 1 administration of MCNA at 8 mg in the Phase 3 studies. In order to compare benefit to risk, safety results focus on the 129 patients treated in Study 301.

In Study 301, regardless of study drug relationship, treatment-emergent local adverse events reported for at least 10% of patients included hematuria, dysuria, urinary tract infection, pollakiuria (increased urinary frequency), and micturition urgency. The most common systemic adverse event was fatigue.

Four patients (3.1%) in Study 301 had adverse events during the study treatment phase that resulted in death but none of the deaths were considered to be drug-related by the investigators.

Among the 129 patients who received MCNA in Study 301, 18 patients reported 32 serious adverse events during the period from the first dose of MCNA until 35 days after the last dose. Serious adverse events reported by more than 1 patient in Study 301 were hematuria (3 patients), syncope (2 patients), and chronic obstructive pulmonary disease (2 patients).

### **Benefit-Risk Summary**

Currently, patients with high risk NMIBC are offered only ineffective and unproven treatments or radical cystectomy as the next treatment following BCG failure. Bladder removal is a complex surgery associated with at least 28% to 45% surgical complications and up to 8% mortality, in addition to negatively impacting multiple aspects of quality of life. Patients who refuse or are not medically fit to undergo bladder removal face an increased risk of progression to muscle-invasive disease, likely leading to metastases and death. MCNA offers a new therapeutic option for these patients.

MCNA preserves the patient's bladder without evidence of disease, thus delaying radical cystectomy. In Study 301, 1 in 4 high risk unresponsive bladder cancer patients were disease-free at 1 year, and these patients experienced a long lasting response, preserving the bladder for approximately 3 years.

An important goal in the surveillance and management of high grade NMIBC is to detect progression to muscle-invasive disease at an early time point. For MCNA, we are able to predict reliably using the Month 6 findings. For patients who responded to treatment at 6 months, approximately 85% remained disease-free or have only non-muscle-invasive recurrences by 3 years. Importantly, if a patient did not respond to MCNA at 6 months, the rate of progression was approximately 25% after 3 years, which is similar to historical data, estimated to be 10 to 15% per year, or 30 to 45% after 3 years.

Finally, in comparison to valrubicin, which remains the only FDA-approved non-surgical option for patients with CIS in whom BCG has failed, MCNA was shown to have higher complete response rates in a comparable patient population.

The key challenges in generalizing the efficacy, duration, and safety of MCNA to the larger target population are that Study 301 was a single-arm study, the study included patients with CIS and/or papillary tumors, and the number of patients limits the ability to confidently estimate efficacy in clinically important subpopulations.

With respect to safety and tolerability, the majority of local adverse events were mild to moderate, manageable, and clearly unlike the complications and risks of radical cystectomy. Common local adverse events included hematuria, dysuria, urinary tract infection, pollakiuria (increased urinary frequency), and micturition urgency.

No death was considered by the investigators to be drug-related. Based on safety data from both trials, bladder-related serious adverse events included urinary tract infection, hematuria, bladder spasm, and bladder perforation (reported > 30 days after the final dose of MCNA).

The incidence of adverse events with MCNA compares favorably to that reported for valrubicin, despite the considerably longer follow up for MCNA. Indeed, the median duration of follow-up from the time of the first dose of treatment to the last evaluation/contact, regardless of response to MCNA treatment, was 34.7 months for the 129 treated patients (range of 0.9 to 60.3 months). Also in contrast to valrubicin, MCNA can

be administered to patients with compromised integrity of the bladder mucosa (e.g., immediately following resection).

Regarding the use of a single-arm study, most experts in the field, including those at the 2013 FDA/American Urological Association (AUA) workshop, have concluded that a single-arm design could provide sufficient evidence of benefit, provided that the results were robust. There was also broad consensus at the workshop that studies might include a mix of patients with high grade papillary disease, CIS, and both. This consensus arose from the significant recruitment challenges posed by this patient population. Recognizing the current sample size limitations, Telesta is committed to working with the FDA to establish more firmly the risk-benefit profile of MCNA.

In summary, despite the substantial burden of bladder cancer in the United States, no new intravesical treatments for NMIBC have been approved since valrubicin in 1998. Given that the current therapeutic landscape provides patients with limited and difficult choices and provides clinicians with little flexibility other than moving to radical cystectomy, new treatment options are urgently needed for patients following BCG failure.

### **Conclusion**

MCNA, with its ability to preserve the bladder for 1 out of 4 patients safely and effectively for approximately 3 years, coupled with its relatively benign toxicity profile, provides a significant clinically beneficial treatment option for patients faced with a paucity of choices and a potentially life-altering and life-threatening disease.

## 1 INTRODUCTION

Telesta has focused its clinical program on developing a new intravesical treatment for adult non-muscle-invasive bladder cancer (NMIBC) patients at high risk of recurrence or progression to muscle-invasive and/or metastatic disease following the failure of bacillus Calmette-Guérin (BCG) immunotherapy (e.g., BCG refractory or BCG relapsing) as a therapeutic option that can delay or avoid radical cystectomy.

**Proposed Indication:** Intravesical use in the treatment of NMIBC at high risk of recurrence or progression in adult patients who failed prior BCG immunotherapy, e.g., in patients who are BCG refractory or BCG relapsing.

## 2 BLADDER CANCER

### 2.1 Disease Background and Pathology

Bladder cancer is a complex disease with different tumor types arising from distinct urothelial cellular characteristics. The tumors are characterized generally (by urologists, as well as by pathologists and radiologists) as NMIBC or muscle-invasive bladder cancer, which includes metastatic disease. Approximately 70 to 75% of newly diagnosed patients are diagnosed with NMIBC [AUA 2014].

Bladder cancer is the most common malignant tumor in the urinary tract, accounting for over 4.5% of all new cases of cancer in the United States [SEER Database]. In the United States, the estimated number of new cases of bladder cancer in 2015 is 74,000 and the estimated number of bladder cancer-related deaths is 16,000 [Siegel 2015]. It is the 4<sup>th</sup> most common cancer in men and the 12<sup>th</sup> in women [ACS 2015]. According to the latest prevalence number, there are close to 600,000 people living with bladder cancer in the United States [SEER Database]. On a lifetime, per-patient basis, it is expected that bladder cancer will continue to be the most expensive cancer to treat [Yeung 2014]. Diagnosis, treatment, and continued surveillance all contribute to the economic burden of bladder cancer [Avritscher 2006, James 2013].

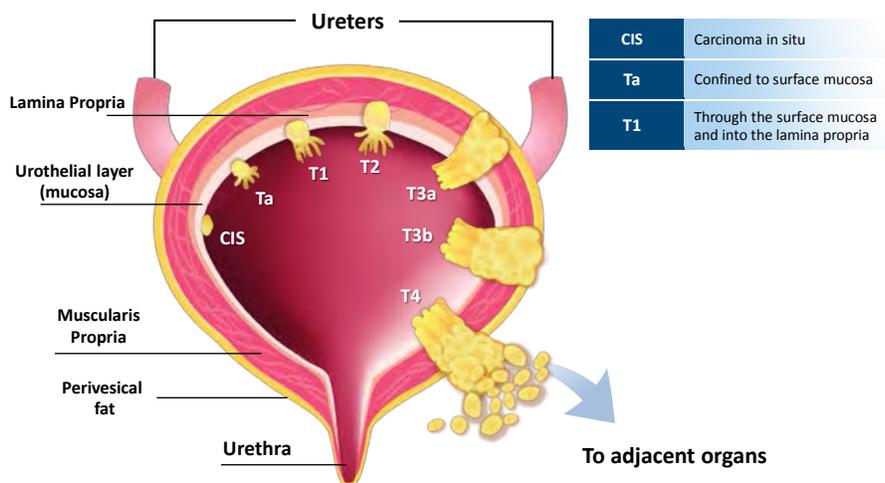
Most bladder cancers are diagnosed in older individuals, with > 90% of patients more than 55 years of age and a median age of 73 years at diagnosis [SEER Database]. Bladder cancer is estimated to be 4 times more common in men than women, and Caucasian-Americans have approximately a 2-fold greater risk compared with African-Americans. Epidemiological evidence has consistently suggested a role for environmental factors (e.g., cigarette smoke and environmental and occupational carcinogen exposure).

Hematuria is the presenting symptom in the majority of patients with bladder cancer. It may be gross or microscopic, and intermittent rather than constant. In a smaller percentage of patients, it is accompanied by symptoms of bladder irritability (i.e., urinary frequency and urgency, as well as dysuria) [AUA 2014]. These symptoms are not specific to bladder cancer, and may be misinterpreted to be urinary tract infections, stones, or other concurrent conditions. Thus, referral to the urologist may be delayed.

Bladder cancer comes in many different forms, with stage and grade as the most important distinguishing features. Both characteristics are important prognostic factors in bladder cancer and guide the clinician's treatment recommendations.

Bladder tumors can be staged according to their depth of invasion in the bladder by using the TNM Classification of Malignant Tumours (Figure 1) [AJCC 2002].

**Figure 1. Bladder Cancer Staging**



Stages Ta, T1, and CIS represent 3 stages of NMIBC tumors and are defined as follows:

- Stage Ta: Papillary tumors are confined to the urothelium (surface mucosa). A papillary carcinoma is a malignant neoplasm characterized by the formation of many irregular, fingerlike projections of fibrous stroma covered with a layer of neoplastic epithelial cells.
- Stage T1: Papillary or sessile tumors have invaded the sub-mucosa (also called the lamina propria). Sessile tumors are attached directly by the base. Polyps that tend to grow as slightly flattened, broad-based polyps are referred to as sessile.
- CIS (also called stage Tis): Flat mucosal cancer is confined to the urothelium and may be focal or diffuse and isolated or associated with papillary tumors. The tumor is high grade by definition. Transurethral resection is not considered effective for CIS disease because it may often be diffuse and difficult to adequately visualize, making complete surgical removal infeasible.

Stages T2, T3, and T4 correspond to muscle-invasive or metastatic bladder tumor.

Bladder cancer can also be described in terms of grade, by which the tumors are evaluated based on their cytologic and/or growth pattern characteristics. Multiple grading schemes have been developed and used throughout the years. In all classifications, lesions that cytologically resemble normal urothelium are lower grade or well-differentiated, whereas cytologic anaplasia is characterized as higher grade or poorly differentiated [Reuter 2006].

The first generally accepted grading classification, the 1973 World Health Organization (WHO) classification, distinguished papillomas (benign tumors) from urothelial carcinoma of grades I, II, and III. More recently, the 2004 WHO classification [Epstein 1998,

[Epstein 2003](#)] recommends changing bladder cancer grading to only 2 categories: 1) well-differentiated or low grade, and 2) poorly differentiated or high grade, as well as having a papilloma and a newly created diagnostic category of papillary urothelial neoplasm of low malignant potential (PUNLMP). This new category was created to avoid labeling a patient as having cancer with its psychosocial and financial (i.e., insurance) implications, although they are not diagnosed as having a benign lesion (i.e., papilloma), whereby they might not be followed as closely [[Epstein 2003](#)].

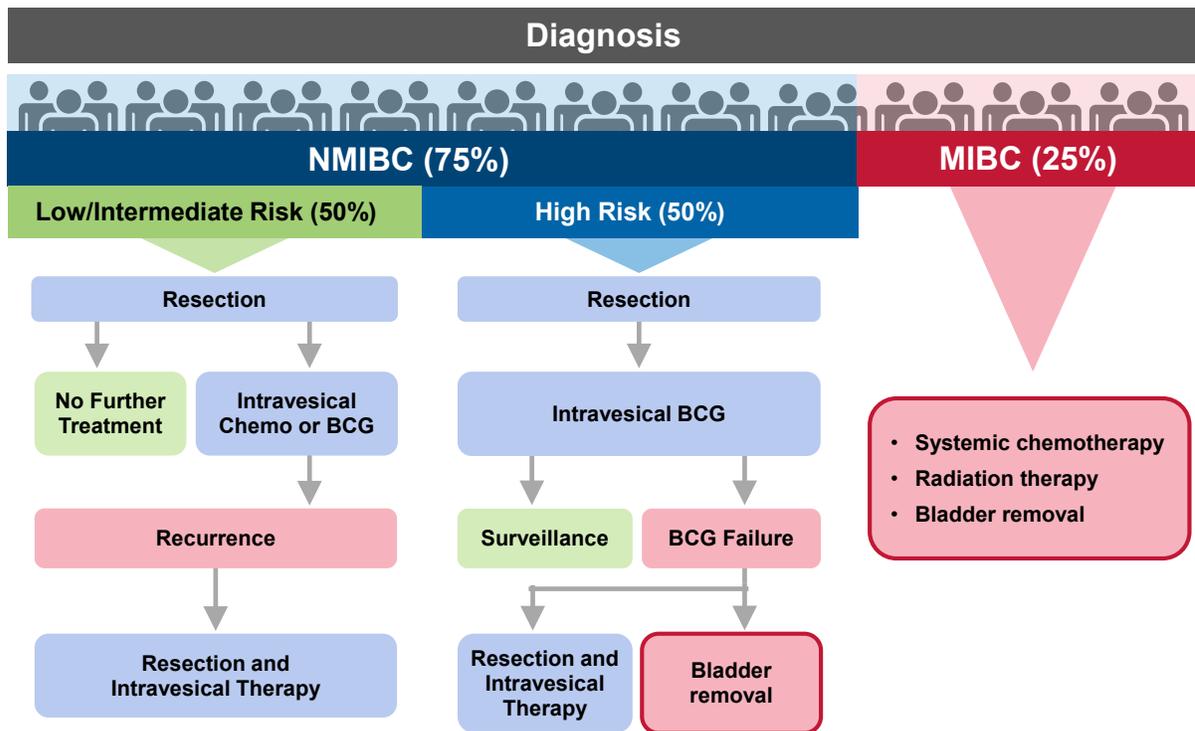
In terms of relationship between the 1973 and 2004 WHO classifications, papilloma is the same for both; Grade I (1973) is split into either PUNLMP or low grade (2004); Grade II (1973) is split into either low or high grade (2004); and Grade III (1973) is high grade (2004).

## **2.2 Therapeutic Landscape for Non-Muscle-Invasive Bladder Cancer (NMIBC)**

The treatment paradigm for high grade NMIBC has been essentially unchanged for decades. The top priority for urologists is to prevent NMIBC from becoming muscle-invasive and/or metastatic, which has a poor survival prognosis. Only 3 types of non-surgical therapy for NMIBC have been approved in the United States since 1959 (thiotepa in 1959, BCG in 1989, and valrubicin in 1998). Thus, there is a significant unmet need for new treatments for NMIBC, especially for patients in whom BCG has failed.

The choice of treatment for NMIBC is guided by several factors but most importantly according to the risk of progression to muscle-invasive and/or metastatic disease, where the opportunities for cure are diminished. A decision schematic for the treatment of bladder cancer is illustrated in [Figure 2](#).

**Figure 2. Decision Schematic for the Treatment of Bladder Cancer**



BCG = bacillus Calmette-Guérin; MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle-invasive bladder cancer

Treatments for NMIBC are primarily surgical or pharmacotherapy localized to the bladder. The surgical resection (also known as transurethral resection of the bladder tumor) provides diagnostic and prognostic information, and may often be therapeutic in papillary NMIBC. Resection can be followed by selective intravesical chemotherapy or immunotherapy.

Intravesical treatments are administered directly into the bladder via a catheter (i.e., intravesical therapy) and may consist of chemotherapy, such as epirubicin, mitomycin C or adriamycin, or more effective immunotherapy, such as BCG.

Choice of treatment depends on the level of risk for progression to muscle-invasion and/or metastases.

**Low Risk**

For patients at low risk of progression, the AUA guidelines recommend treatment with resection, followed by surveillance or a single dose of intravesical chemotherapy (primarily mitomycin C) [AUA 2014]. When administered immediately following resection, the chemotherapeutic agent is thought to prevent tumor cell seeding and implantation and to reduce the risk of recurrence and progression, particularly for low-risk tumors.

**Intermediate Risk**

Patients presenting with intermediate risk of progression (multifocal, large tumor volume of recurrent, stage Ta disease of low grade) are recommended to receive an induction course of

either intravesical BCG immunotherapy or chemotherapy with optional maintenance therapy [[Kamat 2014a](#)].

### **High Risk**

Among patients with high risk of progression, BCG is the treatment of choice. It is also imperative to confirm after an initial resection that all tumors have been removed. Thus in patients with high-risk disease (i.e., high grade, T1 papillary tumors), performing a repeat resection is recommended by the AUA [[AUA 2014](#)].

### **Treatment with BCG**

BCG is recommended in conjunction with resection for high risk patients (CIS and/or Ta or T1 papillary tumors), especially those with CIS. BCG is a live, attenuated strain of *Mycobacterium bovis* that has been used since 1976 to treat NMIBC [[Morales 1976](#)]. While the precise mechanism for BCG efficacy is unknown, it creates a local, non-specific inflammatory and immune response (e.g., involving the release of various cytokines, tumor necrosis factor, interferon gamma, and interleukins). It also induces cytotoxic T cells, macrophages, and natural killer cells, potentially to eliminate tumor recurrences and/or progression.

If BCG fails in a patient with high grade NMIBC, or disease recurs, or progresses to muscle-invasive disease, the standard recommended therapeutic approach is radical cystectomy (i.e., surgical removal of the bladder and surrounding organs) with accompanying urinary diversion. Standard of care for approximately 25% of the patients who are initially diagnosed with muscle-invasive bladder cancer is also radical cystectomy, at times combined with systemic peri-operative chemotherapy, or induction by radiosensitizing chemotherapy in conjunction with radiotherapy.

The superiority of BCG to intravesical chemotherapy in preventing recurrences of bladder cancer in patients with high risk tumors has been demonstrated in multiple studies [[Bohle 2003](#)]. Thus, BCG is recommended as standard of care for the treatment of NMIBC at high risk of recurrence and/or progression [[Clark 2013](#), [Davis 2002](#), [Sylvester 2002](#)]. Treatment with BCG consists of at least an induction course of 6 intravesical doses followed by maintenance therapy as a number of studies and meta-analyses have shown [[Sylvester 2002](#), [Han 2006](#), [Kamat 2014b](#)]. The optimal schedule and duration of maintenance therapy are unknown, although the recommended regimen includes 3 weekly instillations at 3 months, 6 months, and then every 6 months thereafter for at least 1 year and up to 3 years [[Lamm 2000](#)]. Recent studies have demonstrated that 3 weekly instillations are more effective than single instillation maintenance therapy [[Kamat 2014b](#)].

There is also concern about the safety of BCG since it is a live attenuated mycobacterial vaccine and carries the potential for proliferation, dissemination, and sepsis when administered in the presence of disrupted bladder mucosa (e.g., following resection) or traumatic urethral/bladder catheterization [[Lamm 1989](#)]. As such, about 10 days must elapse before BCG is administered following resection, biopsy, or traumatic catheterization. It is considered a biohazardous, infectious material that requires preparation under a hood and the use of gloves, mask, and gown by persons reconstituting and administering it. Furthermore, patients are recommended to void in a sitting position and to use bleach every time they

urinate for 6 hours after treatment so as to prevent contamination. This represents a safety risk for health care professionals and patients, as well as an environmental risk.

### **BCG Failure**

When BCG is used as first-line therapy for high grade NMIBC, approximately 70% of patients respond initially, but 30 to 50% of these responders eventually develop recurrent tumors, depending on the patients' initial risk profiles, amount of BCG received, and follow-up time [Lamm 2000]. There is only 1 FDA-approved non-surgical treatment option available for patients with CIS for whom BCG has failed, namely valrubicin. Urologists currently try multiple non-FDA-approved therapies which have limited, documented efficacy.

### **Radical Cystectomy**

Although current AUA and National Comprehensive Cancer Network guidelines recommend bladder removal for patients with high risk NMIBC as the treatment of choice following BCG failure [AUA 2014, Clark 2013], many patients are not suitable candidates for bladder removal due to co-existing multiple comorbid medical illnesses and the difficulty of recovery from surgery (particularly in older patients).

In both men and women, cystectomy involves a bilateral pelvic lymphadenectomy and removal of the bladder, peritoneal covering, perivascular fat, and distal ureters. In the male patient, the prostate, seminal vesicles, and vas deferentia are also removed; whereas in the female patient, removal of the cervix, uterus, fallopian tubes, ovaries, and a segment of the anterior vaginal wall is required.

Radical cystectomy is a complex surgery, requiring 6 to 8 hours under anesthesia, 5 to 10 days in the hospital, and a 6- to 8-week recovery period. The procedure is associated with at least 28% to 45% surgical complications and 2% to 3% mortality, with up to 8% mortality within 6 months of surgery in the elderly population [Hollenbeck 2007]. Possible complications can be gastrointestinal (e.g., ileus and small bowel obstruction), cardiac, genitourinary (e.g., deterioration of renal function), pulmonary, thromboembolic (e.g., deep vein thrombosis), neurologic (e.g., paralysis), and can also include infections, bleeding, stone formation, loss of sexual function, blockage of urine flow from the ureters to the bladder, stomal problems, and accidental urinary leakage and incontinence. In a review of 1142 consecutive patients with radical cystectomy, 64% of patients experienced 1 or more complications within 90 days following surgery. Of those, 83% had complications classified as grade 2 to 5 [Donat 2009]. Hospital readmission for surgery-related complications was required in 26% of patients during the 90 days following surgery, and 34% of patients required emergency room visits.

Peri- and post-surgical complications from radical cystectomy are not the only impact on patients' lives. Following radical cystectomy, urinary diversion is required. Urinary tract diversions are separated into 2 standard categories: continent and incontinent diversions, which necessitate external ostomy collecting devices. There are 3 primary options for urinary diversions:

- Orthotopic neobladder (continent): This option does not require an external stoma. However, the patient must be educated and compliant with a labor-intensive rehabilitation process and must be able to perform self-catheterization, if necessary.
- Continent cutaneous reservoir: When an orthotopic neobladder is not appropriate, this procedure may provide another continent option. An external appliance is not required, but clean intermittent self-catheterization through the stoma is necessary to empty the reservoir and irrigate retained mucus.
- Ileal conduits (incontinent): This option remains the procedure of choice for patients with contraindications to continent diversion. The use of urine collecting bags is cumbersome and patients face a lifetime of external urine collecting devices and/or continence pads.

The cumulative consequences of radical cystectomy and urinary diversion are life-altering and reduce the ability of patients to continue previously normal daily tasks. Therefore, many patients refuse to consider cystectomy due to concerns about quality of life, urinary continence or ostomy, as well as sexual dysfunction.

### **Valrubicin**

Valrubicin (Valstar<sup>®</sup>) is approved in the United States for intravesical therapy of BCG refractory CIS of the urinary bladder in patients for whom immediate cystectomy would be associated with unacceptable morbidity or mortality [[Endo 2011](#)]. In its single registration study of 90 patients with BCG refractory CIS disease, 18% of patients had a complete response 6 months after starting treatment [[Steinberg 2000](#)].

### **Other Agents**

After BCG failure, many patients receive additional intravesical therapies, including more BCG, rather than undergoing bladder removal. The potential risks of this approach are substantial. In an historical cohort of 307 patients from 3 prospective protocols from 1980 to 1989, 85 (28%) patients had documented T1 recurrence over a 4-year follow-up after BCG therapy [[Raj 2007](#)]. These patients had been treated with repeat resection and intravesical BCG. Of these 85 patients, 60 subsequently progressed to muscle-invasive disease. An actuarial analysis of repeated courses of BCG treatment identified a 7% risk of developing muscle-invasive disease at entry into BCG therapy [[Catalona 1987](#)]. In patients who failed to respond to 2 courses of BCG, the risk of metastatic cancer exceeded the probability of tumor eradication with BCG.

Since the approval of valrubicin in 1998, no new intravesical treatments for NMIBC, including patients for whom BCG has failed, have been approved by the FDA. As such, patients with NMIBC are often only 1 treatment failure away from bladder removal. Given that the current therapeutic landscape provides patients with difficult choices and provides

clinicians with little flexibility, new treatment options are needed for patients following BCG failure.

### **2.3 Development Challenges for Treatments of NMIBC**

The Telesta development program was faced with several difficulties in defining study design, patient eligibility criteria, and efficacy endpoints. The approval of only 3 types of non-surgical therapy in the United States since 1959 (thiotepa in 1959, BCG in 1989, and valrubicin in 1998) provides evidence of these challenges. These problems were discussed in a 2013 public workshop hosted by the FDA and the AUA, with the goal of facilitating the development of new therapies for NMIBC [Jarow 2014]. This workshop was intended to highlight the opportunities and challenges in bladder cancer research and did not represent FDA policy or guidance.

The workshop panel recommended to the FDA that single-arm pivotal studies for high risk NMIBC could provide sufficient evidence of benefit, provided that the results were robust. There was broad consensus that studies might include a mix of patients with high grade papillary disease, CIS, and both.

The workshop panel gave several reasons for proposing a single-arm pivotal study for all NMIBC high grade patients. First, there is no suitable comparator for an active-controlled study. Bladder removal may not be an appropriate comparator because patients cannot be randomized into bladder removal without their explicit approval and consent.

Other agents, such as mitomycin C and valrubicin, also present shortcomings as potential comparators.

For mitomycin C, most of the persuasive data and results involved combination therapies of mitomycin C with other types of thermo- or electrotherapy. For valrubicin, the only FDA-approved non-surgical therapy for patients with BCG refractory CIS, the low adoption rate among physicians in the United States suggests that many physicians are not enthusiastic about using it. This reluctance may be due to low durable response rates and similar disease progression as other intravesical agents. Presently, there is no therapy that provides significant durable responses; thus, patients in the control group would be subject to a high risk of disease progression in a randomized trial. Most investigators view this as unethical treatment for young and medically fit patients.

The preferred primary endpoint suggested by the panel for a single-arm pivotal study was time to event using failure to achieve a complete response in patients with CIS and recurrence in patients with CIS or papillary disease as the events. For patients with BCG refractory CIS, the panel felt that an initial complete response rate of 40% to 50% at 6 months and a durable response rate of at least 30% for 18 to 24 months, with the lower bound of the 95% confidence interval excluding 20%, could be clinically meaningful. However, these suggested criteria should not be considered as a minimal efficacy requirement for therapies being evaluated for approval. In fact, the proposed response rates and lower confidence bound have never been achieved with any agent to date. The totality of evidence, including other clinical benefits and lack of serious side effects, must also be considered.

There was no discussion of what would be an acceptable level of response/recurrence-free interval for patients with BCG refractory papillary disease without CIS.

A randomized trial may also skew the patient population toward a non-representative cohort of NMIBC patients because physicians recognize the risk of enrolling and placing a patient in a potentially inferior control arm of the study and the significant risk of disease progression. This may result in physicians recommending bladder removal for medically fit patients and only enrolling medically unfit patients for study (i.e., much older patients with multiple comorbidities and those with potentially non-robust immune systems). This population of NMIBC patients may not be representative of the whole population and may not serve as a reliable indicator of the drug's efficacy and durability in the overall high risk NMIBC patient population.

In addition, this combination of a small target population and institutional resistance to the potential comparators will likely lead to lengthy enrollment periods for a randomized trial. Lengthy enrollment periods (e.g., > 5 years) may have deleterious effects on the consistency of study results over the duration of enrollment.

Recruitment can be improved by supplementing the population of BCG refractory CIS patients with high-risk papillary NMIBC patients. A combination of high grade papillary Ta and T1 tumors and/or CIS patients into a single trial is appropriate because these patients have very similar recurrence and progression rates. Furthermore, many Ta and T1 tumors may start as CIS, or have CIS concomitantly which may be undetected by current diagnostic methods (mainly white light cystoscopy). Newer methods, such as narrow band imaging and blue light cystoscopy, may detect CIS in 20 to 25% of patients not detected by white light. [Zheng 2012, Oude Elferink 2014]. Finally, in many patients, bladder cancer is a monoclonal disease (i.e., CIS, Ta, and T1 cells are clones from the same bladder tumor initiating cells) suggesting many shared similarities in malignant behavior in high risk NMIBC.

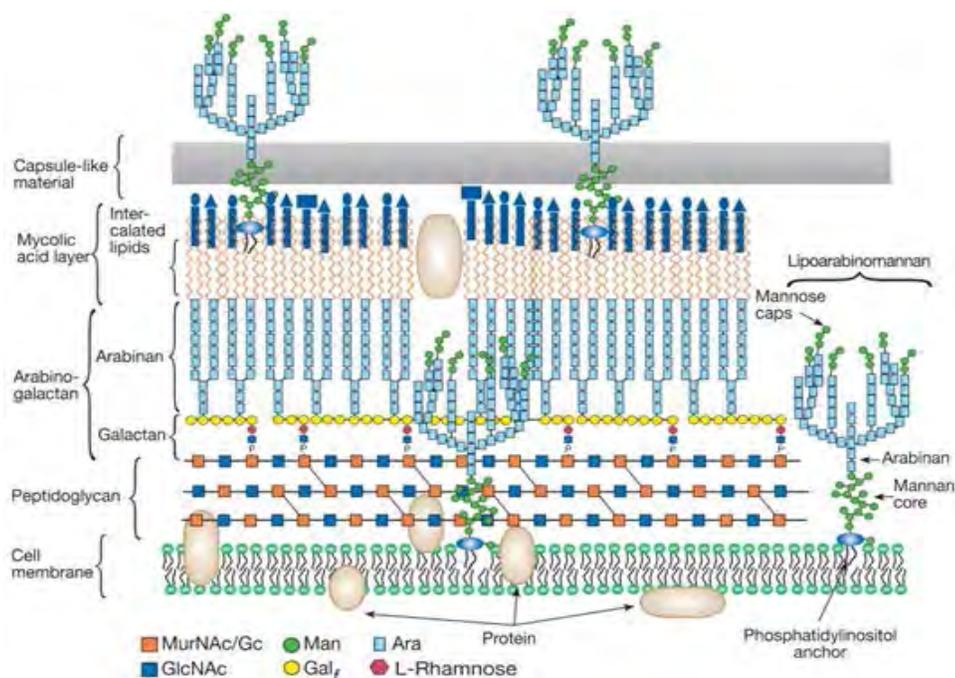
#### **2.4 Background on Mycobacterium phlei Cell Wall-Nucleic Acid Complex**

Telesta focused on using a novel agent, MCNA, in its clinical development program in bladder cancer. The source organism for MCNA, *Mycobacterium phlei*, is a ubiquitous, non-infectious mycobacteria found widely in the environment including tap water and soil. *Mycobacterium phlei* is not a recognized pathogen for any species, including mammals [Filion 2001].

MCNA suspension is an immunomodulator/anti-proliferative biological product manufactured by a proprietary process involving disruption of *Mycobacterium phlei* cell walls (Figure 3) by repeated microfluidization and refinement steps to the final sterilized product.

Figure 3 shows the complexities of the mycobacterial cell wall, the fragmented components of which are present in the final MCNA composition.

**Figure 3. Stylized Illustration of Mycobacterial Cell Wall**

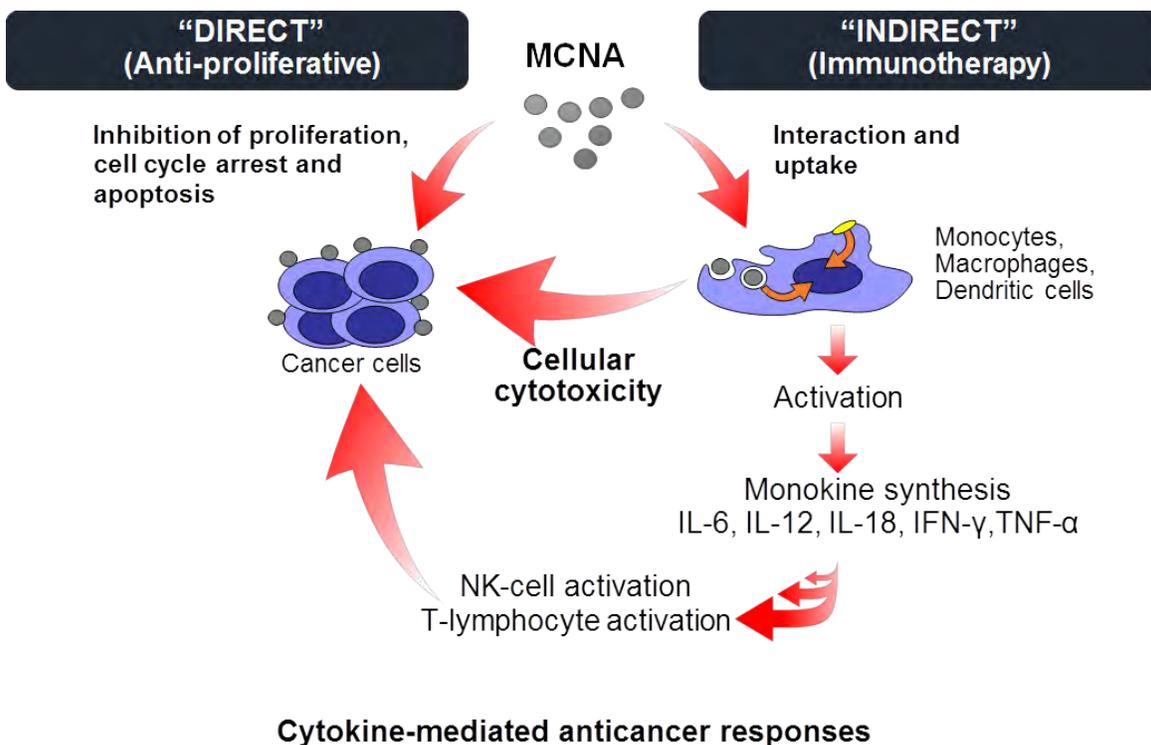


The MCNA product carries a number of immunomodulatory constituents such as trehalose dimycolates, lipoproteins, peptidoglycans, and lipoglycans. The disruption process presumably increases the surface area of cell wall constituents, allowing for enhancement of the immunostimulatory response by making the cellular constituents responsible for activity more available to immune stimulatory cells and cancer cells.

#### **2.4.1 Proposed Mechanism of Action for MCNA**

Current evidence suggests that MCNA induces its anti-bladder cancer effect by a dual mechanism, an indirect immunomodulatory stimulation and a direct anti-proliferative/cytotoxic action (Figure 4).

**Figure 4. Dual Mechanism of Action for MCNA**



IFN = interferon; IL = interleukin; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; NK = natural killer; TNF = tumor necrosis factor

While the precise indirect mechanisms for MCNA efficacy are not completely established, it is thought to create local, non-specific inflammatory and immune responses to prevent bladder tumor recurrences and/or progression to muscle-invasive or metastatic disease. The indirect, immune stimulant activity of MCNA is linked to monocytic cell activation, namely dendritic cells and macrophages. Mechanistically, MCNA induces known anticancer immune regulatory cytokines and chemokines, including interleukin (IL)-6, IL-10, IL-12, IL-18, interferon- $\gamma$ , and tumor necrosis factor- $\alpha$ . Although the indirect immune modulatory mechanism of action of MCNA has not been fully elucidated, the activation of toll-like receptor 2 and nucleotide-binding oligomerization domain-containing protein 2 receptors of the innate immune response implicate a partial mechanistic pathway for the activation of mononuclear immune cells and cytokine induction.

The direct anti-proliferative action against bladder cancer cell lines is characterized by inhibition of proliferation, cell cycle arrest, and induction of apoptosis, manifested through modification of intracellular signaling pathways.

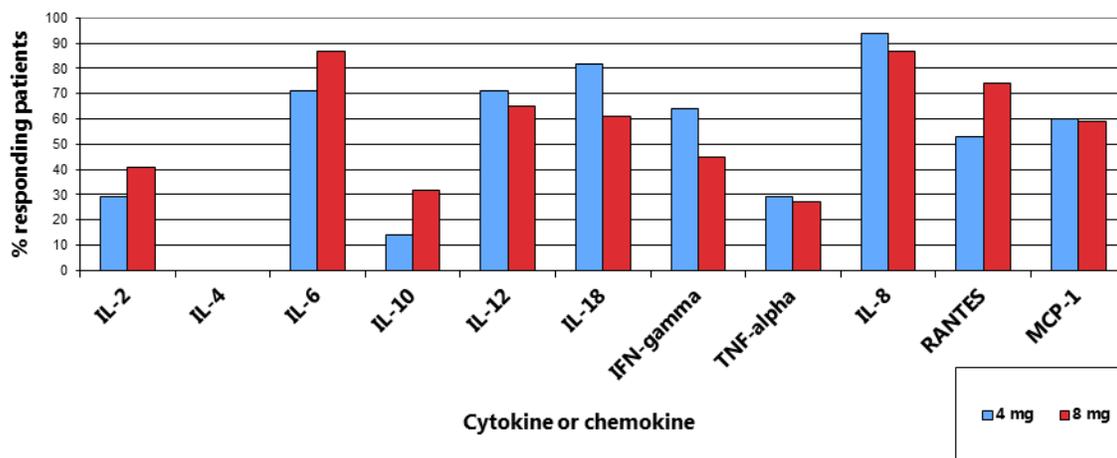
Complementary evidence for the immunostimulatory mechanism comes from *in vitro* studies on mononuclear cells and *ex vivo* testing using human peripheral blood mononuclear cells from both normal volunteers and patients with transitional cell carcinoma, wherein induction of cytokines and chemokines characteristic of a Th1 immune response was detected. Concentration- and time-dependent cytokine induction has been demonstrated in a range of human, monkey, canine, rat, and murine cell types *in vitro* and *in vivo*, and the elicited

cytokine profile is consistent with MCNA suspension acting on macrophages, monocytic, and dendritic cells. MCNA also induced cytokine synthesis following systemic administration in rodents, Beagle dogs, and Cynomolgus monkeys.

Clinical evidence is provided by urinary concentrations of proinflammatory cytokines, detected in BCG refractory patients with CIS following treatment with an MCNA predecessor product (Mycobacterial Cell Wall-DNA Complex [MCC] Emulsion) in Study 9708. Patients were treated with 4 or 8 mg of MCC Emulsion once weekly for 6 weeks, as part of Study 9708. Urines were analyzed for the presence of cytokines (IL-2, IL-4, IL-6, IL-10, IL-12, IL-18, interferon- $\gamma$ , and tumor necrosis factor- $\alpha$ ) and chemokines (IL-8; regulated on activation, normal T expressed and secreted protein; and monocyte chemoattractant protein-1) before treatment, at 3 to 6 hours and at 18 to 24 hours post-treatment after the 3<sup>rd</sup> and 6<sup>th</sup> instillations. Cytokine and chemokine levels were normalized to urinary creatinine levels (pg/mg) to eliminate differences in urine volume. To illustrate the induction of proinflammatory cytokines, the percentages of patients presenting a  $\geq 2$ -fold increase in cytokine or chemokine levels were compared with pretreatment baseline at the 4 and 8 mg dose levels.

The percentages of patients having these vital cytokines present in their bladder post MCC Emulsion treatment are quite high (Figure 5). Clearly, treatment with either 4 or 8 mg causes the increased induction of the cytokines with no dose related effect. Although the array of enhanced urinary cytokines cannot be precisely labeled as representing a Th1 response, the presence of elevated levels of IL-2, IL-12 and IFN- $\gamma$  coupled with the absence of IL-4 is consistent with what is recognized for a Th1-type proinflammatory response.

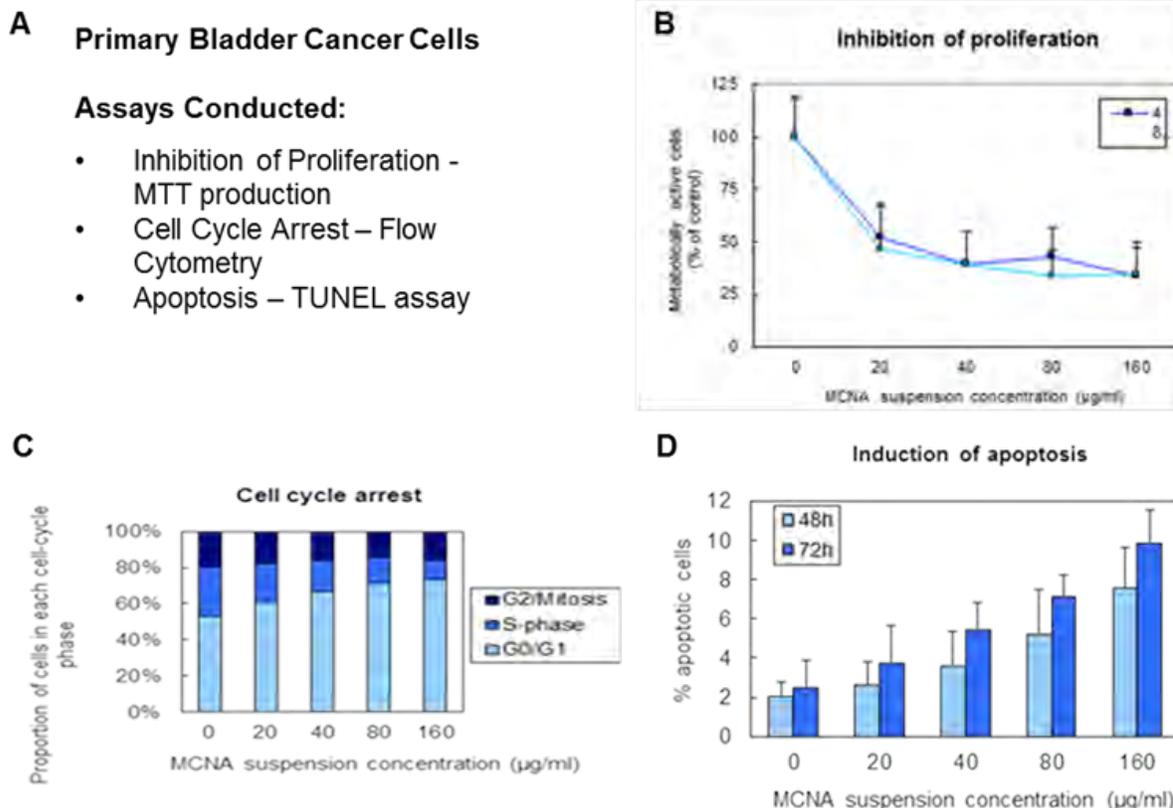
**Figure 5. Urinary Cytokines in Bladder Cancer Patients Following Treatment With an Early MCNA Formulation (MCC Emulsion)**



DNA = deoxyribonucleic acid; MCC = Mycobacterial Cell Wall-DNA Complex; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

The direct anti-proliferative/apoptotic effect of MCNA is demonstrated by *in vitro* experiments showing inhibition of proliferation, induction of cell cycle arrest, and initiation of apoptosis in several human primary bladder cancer cells and cancer cell lines (Figure 6).

**Figure 6. MCNA as an Anti-Proliferative Agent**



MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; TUNEL = terminal deoxynucleotidyl transferase dUTP nick end labeling

*In vitro* studies were conducted to explore the anti-proliferative and cytotoxic activities of increasing concentrations of MCNA in primary bladder tumor cultures, prepared from samples of patients undergoing bladder tumor resections (Figure 6, Panel A).

Cell proliferation was determined using the standard (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) MTT assay, a colorimetric assay for assessing cell metabolic activity, following 48 and 72 hours of exposure to MCNA, as shown in Figure 6, Panel B. MCNA treatment reduced the proliferative capacity of the primary tumor cells to less than 50% of untreated control levels.

The effect of MCNA on cell cycle progression was tested by flow cytometry using propidium iodide, as shown in Figure 6, Panel C. MCNA inhibited cell cycle progression, with an increase in the number of cells in the G<sub>0</sub>/G<sub>1</sub> phase and a concomitant decrease in the number of cells in the S phase of the cell cycle.

The induction of apoptosis following MCNA was assessed using the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay and is shown in [Figure 6](#), Panel D. MCNA induced a significant dose related increase in the number of apoptotic cells after incubations of 48 hours at 80 and 160 µg/mL and 72 hours at 40, 80, and 160 µg/mL.

#### **2.4.2 Non-Clinical Program**

##### **Non-Clinical Pharmacology**

The objectives of the non-clinical pharmacology program were to define the activity profile and to elucidate as clearly as possible the mechanism of action of MCNA as an anti-cancer agent in the urinary bladder. These studies are presented above.

##### **Non-Clinical Pharmacokinetics**

The systemic pharmacokinetic profile of MCNA was studied in dogs following intravenous and intravesical administration. Blood, tissue, and urine levels of MCNA were determined by quantitative real-time polymerase chain reaction detection of MCNA-associated DNA. Based on the physicochemical properties of MCNA and the intravesical route of administration, metabolism and pharmacokinetic drug-interaction studies were not conducted. Following intravesical instillation, the disappearance of MCNA from the urinary bladder is rapid. At 3 and 24 hours post-dose, less than 4% and 0.1%, respectively, of the dose was detected in the urine collected. No detectable levels of MCNA-associated DNA were found in the systemic circulation following intravesical instillation of MCNA to dogs at doses up to 5 times (40 mg) and concentrations up to 6.25 times (1 mg/mL) the clinical dose (8 mg; 0.16 mg/mL).

Following single intravenous bolus doses up to 0.8 mg/kg, MCNA was rapidly cleared from the circulation and was no longer detectable in the blood between 120 to 180 minutes post-dose. The administration of this dose of MCNA was not associated with any significant toxicological effect.

##### **Non-Clinical Toxicology**

The toxicology program was designed to evaluate the safety and tolerability of MCNA by closely reproducing the proposed clinical schedule of MCNA administration. MCNA was administered by intravesical instillation in long term toxicity studies to rats and Beagle dogs once weekly at Weeks 1 to 6 (Induction Phase), followed by treatment at Weeks 10, 14, 18, 22 and 26 (Maintenance Phase). The reversibility of any observed changes was determined after an 8-week Recovery Phase. The dose levels of MCNA used in these long-term safety studies resulted in MCNA bladder concentrations of 1 to 6 times the initial concentration in the bladder of patients on clinical study.

In the rat study, reversible inflammation of the urogenital organs was found to result from catheterization procedures in males and females independent of MCNA or control treatment. MCNA worsened the degree of severity for the procedure-induced inflammation in the urogenital system involving urethra, urinary bladder, kidney, prostate, and seminal vesicles. The incidence and degree of severity of the inflammatory responses were slightly to moderately increased in MCNA-treated rats compared to vehicle controls, but displayed no consistent relationship to dose.

In Beagle dogs, the intravesical instillation procedure over 26 weeks induced minimal, dose related, semi-reversible mucosal inflammation, the incidence and chronic nature of which was elevated in the urinary bladder and urogenital tract of MCNA-treated animals.

### **3 CLINICAL DEVELOPMENT PROGRAM**

The clinical development program for MCNA includes 2 studies with the formulation intended for marketing and 2 historical studies with prior formulations containing mineral oil.

The first 2 proof-of-concept studies (Study 9404 and Study 9708) in the clinical development program were conducted outside of the United States and were therefore not submitted to the United States Investigational New Drug application (IND). Both studies were completed in the 1990's and used early formulations of MCNA that were manufactured using a different process than that used currently.

The first formulation, Mycobacterial Cell Wall Extract (MCWE), was used in Study 9404 and was an oil emulsion containing thimerosal, an organomercury compound that was used as a preservative in vaccines and other products. It was removed from the subsequent formulation (MCC Emulsion), and this formulation was used for Study 9708, which was a dose-response study. MCC Emulsion was also an oil emulsion formulation and contained small amounts of animal proteins that were subsequently removed from the final formulation (MCNA) that is intended for commercialization. MCNA is a terminally sterilized, water-for-injection suspension and does not contain bovine-derived products, phenol, or urea.

The final 2 studies of the clinical development program (Study 301 and Study 303) were conducted in the United States and Canada and were submitted to the United States IND. These 2 studies used the final formulation and manufacturing process for MCNA that is intended for marketing. Study 301 provides the primary evidence for the benefits and risks of MCNA in the treatment of NMIBC in adult patients at high risk of recurrence or progression following the failure of BCG immunotherapy (e.g., BCG refractory or BCG relapsing). Study 303 was terminated early due to slow recruitment, and only 6 patients completed the 1-year treatment (2 on MCNA; 4 on mitomycin C).

A tabular summary of the clinical studies is provided in [Table 1](#). Key regulatory history is provided in [Section 9](#).

**Table 1. Clinical Studies of Mycobacterium Cell Wall Compositions**

Study Countries Years Sites (n/N) <sup>a</sup>	Treatment History	Treatment	Number Dosed	Protocol-Specified Regimen Study Duration
<b>Formulation: MCNA Suspension</b> <b>Population: Carcinoma <i>in situ</i> and/or high grade papillary tumors</b>				
Study 301 US, Canada Completed 2006 to 2012 25/31	<ul style="list-style-type: none"> <li>Failed prior treatment with BCG (refractory or relapsing)</li> </ul>	MCNA 8 mg	129	<b>Induction:</b> 6 weekly administrations <b>Maintenance:</b> 3 or 6 weekly administrations at Month 3 and then 3 weekly administrations each at Months 6, 12, 18, and 24 <b>Duration:</b> 21 to 24 administrations over 2 years with follow-up to Month 60 <b>Retention time for MCNA:</b> Minimum of 120 minutes
Study 303 <sup>b</sup> US, Canada, Poland Terminated early 2010 to 2013 41/88	<ul style="list-style-type: none"> <li>Failed prior treatment with BCG (refractory or relapsing)</li> </ul>	MCNA 8 mg Mitomycin C 40 mg/40 mL	37 45	<b>Induction:</b> 6 weekly administrations <b>Maintenance:</b> 1 monthly administration from Month 3 through Month 12 <b>Duration:</b> 16 administrations over 12 months with follow-up to Month 36 <b>Retention time for MCNA:</b> Minimum of 60 minutes
<b>Formulation: MCWE Emulsion (Regressin<sup>®</sup>)</b> <b>Population: Carcinoma <i>in situ</i> with or without papillary tumors</b>				
Study 9404 Canada Completed 1992 to 1997 11/11	<ul style="list-style-type: none"> <li>Treatment naïve or</li> <li>Failed or were refractory to BCG therapy and/or intravesical chemotherapy</li> </ul>	MCWE 2 mg MCWE 4 mg MCWE 8 mg MCWE Retreatment <sup>c</sup> 4 mg 4 mg/8 mg	6 58 2  4 5	<b>Induction:</b> 6 weekly administrations <b>Maintenance:</b> 10 monthly administrations <b>Duration:</b> 16 administrations over 12 months with follow-up to Week 78 <b>Retention time for MCWE:</b> Minimum of 120 minutes
<b>Formulation: MCC Emulsion</b> <b>Population: Carcinoma <i>in situ</i> with or without papillary tumors</b>				
Study 9708 Canada, Australia Completed 1999 to 2003 13/13	<ul style="list-style-type: none"> <li>Treatment naïve or</li> <li>Failed prior treatment with BCG therapy and/or intravesical chemotherapy</li> </ul>	4 mg MCC 8 mg MCC	25 30	<b>Induction:</b> 6 weekly administrations <b>Maintenance:</b> 3 weekly administrations at Weeks 12 and 24 <b>Duration:</b> 12 administrations over 26 weeks with follow-up to Month 18 <b>Retention time for MCC:</b> Minimum of 120 minutes

BCG = bacillus Calmette-Guérin; DNA = deoxyribonucleic acid; MCC = Mycobacterial Cell Wall-DNA Complex; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; MCWE = Mycobacterial Cell Wall Extract; US = United States

<sup>a</sup> n = number of sites recruiting patients; N = number of sites initiated.

<sup>b</sup> Study was terminated due to logistical issues related to study design that led to slow recruitment.

<sup>c</sup> Protocol was amended to allow for the retreatment of patients who were considered failures at Week 12 with a first retreatment at 4 mg and a second retreatment at 8 mg (for patients failing the first retreatment).

### 3.1 Rationale for MCNA Dose Selection in the Phase 3 Program

The rationale for clinical dose selection was initially based on pharmacodynamic data. Results included effects on peripheral blood mononuclear cells, cultures of human urinary bladder cancer cells, and *in vivo* pharmacokinetics studies on dogs.

Study 9404 and Study 9708 provided data on patients who received intravesical doses of 2 mg, 4 mg, or 8 mg per administration of predecessor mycobacterial cell wall formulations containing mineral oil. The results from these studies support the proposed dose of 8 mg per administration for MCNA in the Phase 3 program. The 8 mg dose provides an estimated local concentration of 40 to 160 µg/mL, taking into consideration urine production during the 1 to 2 hours that the patient retains the instillate. This is within the concentration range required for maximum induction of the cytokine response and inhibition of bladder cell growth *in vitro*. In addition, results from Study 9708 suggested that the 8 mg dose was slightly more efficacious than the 4 mg dose. The 8 mg dose was well-tolerated in the clinical development program.

### 3.2 Study 301

Study 301 provides the primary evidence for the efficacy and safety of MCNA. Study 301 was an open-label, single-arm, multicenter study of MCNA in patients with NMIBC at high risk of progression and in whom BCG treatment had failed. The first patient was enrolled on 07 November 2006. The last patient completed the study on 03 December 2011. The clinical study report was completed on 18 May 2012. Interim efficacy and safety results at 1 year were presented in 2011 at international urology association meetings and study results were published in 2015 [[Morales 2015](#)].

#### Eligibility

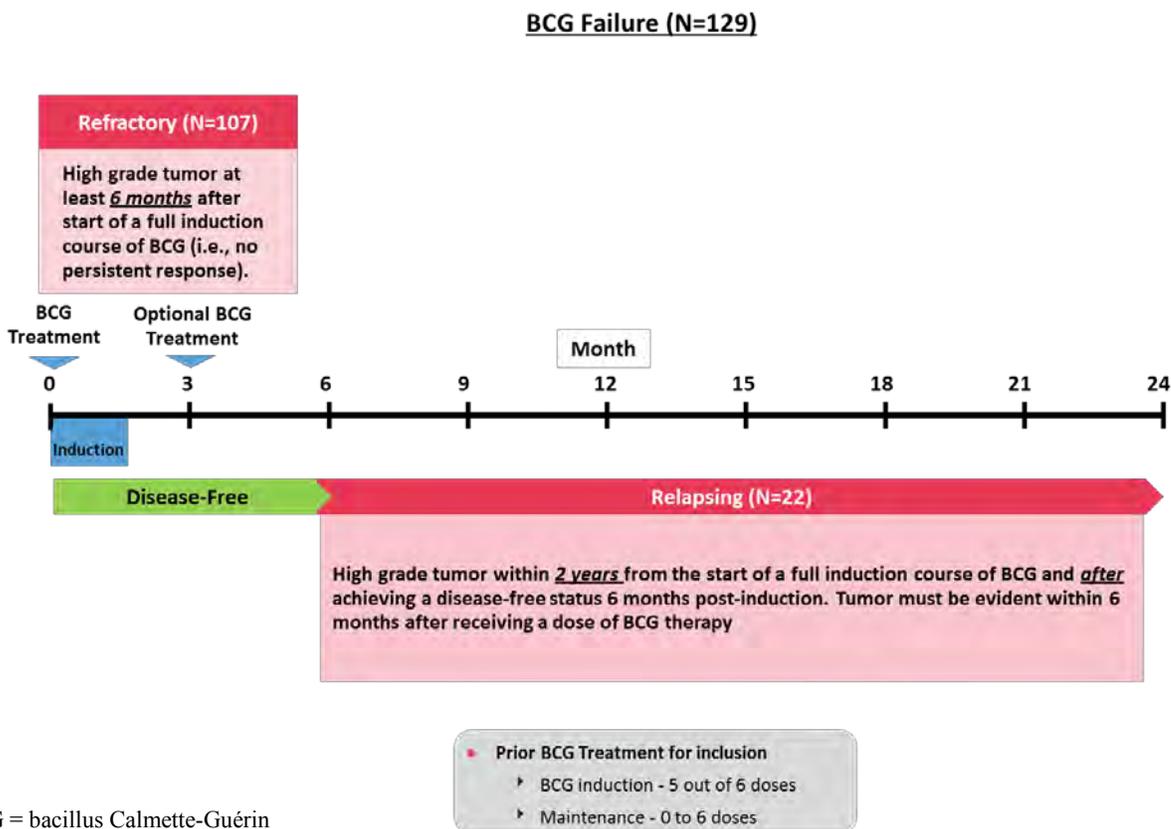
For enrollment in Study 301, patients must have had a histologically confirmed diagnosis of high grade NMIBC according to the local pathologist, i.e., presence of CIS with or without Ta or T1 papillary tumor(s) of any grade or high grade Ta or T1 papillary tumors only. A histologically confirmed diagnosis of high grade disease and resection of papillary lesions by resection, if applicable, must have had occurred within 56 days prior to the beginning of treatment. While the resection/biopsy eligibility material was sent to a central pathologist for review, entry into the study was based on the local pathologist's diagnosis of high grade disease. Patients who were considered eligible according to the local pathologist were allowed to remain in the study even if the central pathologist could not confirm the initial grading by the local pathologist.

Patients were also required to be refractory to, or have relapsed following, BCG treatment ([Figure 7](#)). BCG refractory was defined as evidence of persistent high grade bladder cancer after at least 6 months had elapsed following the start of a full induction course of BCG with or without maintenance/re-treatment at 3 months.

BCG relapsing was defined as evidence of high grade bladder cancer within 2 years from the start of a full induction course of BCG and after achieving a disease-free status 6 months post-induction. The relapsing tumor must have been evident within 6 months after receiving a dose of BCG therapy. These populations, currently described as BCG unresponsive, are

understood to be associated with the highest risk for progression to muscle-invasive or metastatic disease and are not indicated for further BCG therapy [Lerner 2015].

**Figure 7. Definition of BCG Failure Population (Study 301)**



BCG = bacillus Calmette-Guérin

Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance score of  $\leq 2$  (Section 10) and must have had a life expectancy of  $> 5$  years. The ECOG measures a patient’s level of functioning in terms of their ability for self-care, daily activity, and physical ability. A performance score of 2 corresponds to a patient who is ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours. Patients with current or previous history of muscle-invasive bladder tumors were to be excluded from enrollment. A complete list of entry criteria is presented in Section 11.

### Study Procedures and Dosing

The study was divided into 3 phases (Induction, Maintenance, and Follow-Up; Figure 8). The Induction Phase consisted of the first 6 weeks of the study.

Induction therapy consisted of 1 intravesical instillation each week for 6 consecutive weeks, for a total of 6 induction doses. The maintenance therapy schedule started 6 weeks after completion of the induction therapy. Maintenance therapy consisted of 3 weekly intravesical instillations at Months 3, 6, 12, 18 and 24, following the initiation of the induction treatment, for a total of 15 maintenance doses. At Month 3, induction therapy could have been repeated

(i.e., 6 doses may be given instead of 3). In total, between 21 and 24 instillations of MCNA could have been administered over 24 months.

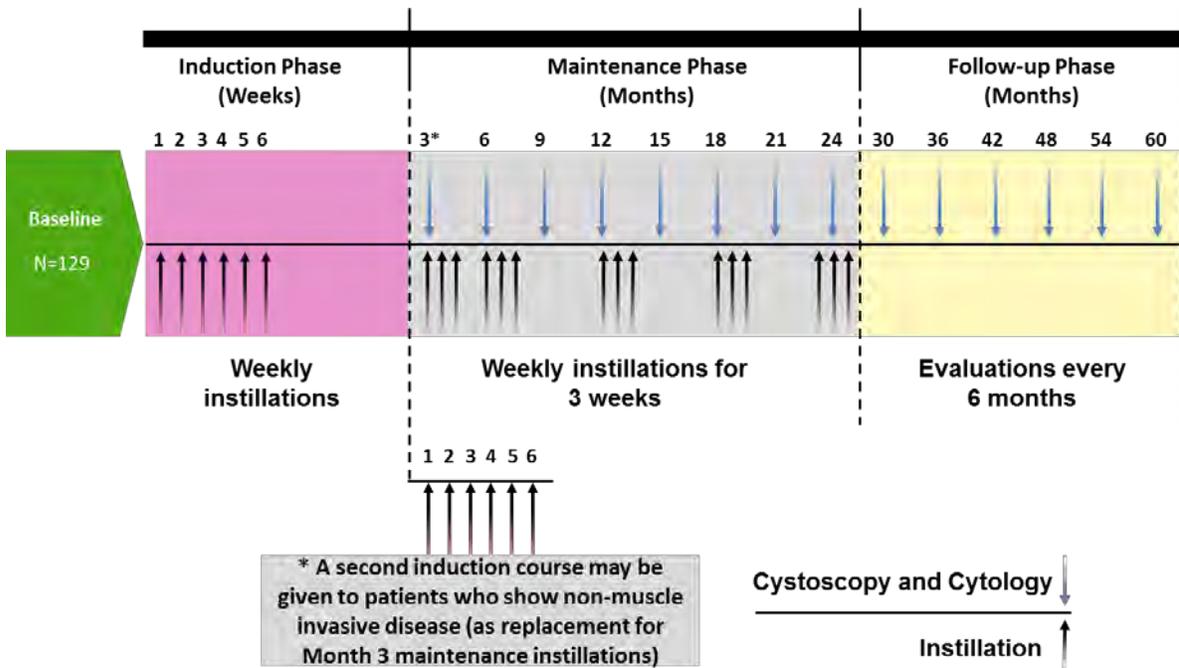
At Month 3, patients were evaluated by standard cystoscopy examination and voided urine cytology. Patients who were tumor-free, or that showed new or ongoing CIS or low grade Ta disease at 3 months were allowed to continue taking the study drug as part of the Maintenance Phase of the study until the Month 6 evaluation.

The Maintenance Phase lasted from Month 3 to Month 24. Evaluations by standard cystoscopy examination and voided urine cytology were performed every 3 months. Mandatory biopsies were performed for all patients at Month 6; this time point was chosen as a safety point to assure no patient progressed.

The Follow-Up Phase lasted from Month 24 up to Month 60. During this phase, evaluations by standard cystoscopy examination and voided urine cytology were performed every 6 months. Information was collected on disease progression, death, and cystectomy.

Resection and bladder biopsies were to be performed during the Maintenance and Follow-Up Phases if the patient had a positive cystoscopy and/or urine cytology. The schedule of procedures is presented in [Section 12.1](#).

**Figure 8. Study Schematic (Study 301)**



The procedure schedule was consistent with that for BCG. For example, a study of BCG by the South West Oncology Group had cystoscopy and urinary cytology repeated for tumor-free patients at 3-month intervals for 2 years, 6-month intervals for 2 years, and yearly thereafter [Lamm 2000]. Patients with CIS disease underwent bladder biopsy at 3 and 6 months, and thereafter only if indicated by suspicious urinary cytology or cystoscopy.

## Efficacy Endpoints

The primary efficacy endpoint was disease-free survival of 40% at 1 year (as a percentage). Time to disease-free survival was defined as the number of days from the first dose of MCNA to recurrence, progression to muscle-invasive disease, or death, whichever came first.

For the primary endpoint, disease-free survival was based on biopsy assessments by a central pathologist. Secondary efficacy endpoints corresponded to the secondary objectives previously identified.

The clinical response during the Maintenance and Follow-Up Phases was defined as follows:

- Recurrence: any diagnosis of NMIBC, or muscle-invasive bladder cancer, as confirmed by biopsy.
- Progression: any diagnosis of muscle-invasive bladder cancer, as confirmed by biopsy.
- Disease-free: no biopsy confirmed evidence of bladder cancer (muscle-invasive or non-muscle-invasive).

Because all NMIBC patients were vulnerable to progression to muscle-invasive disease at study entry, progression-free survival can be measured from Day 0 in all patients. Therefore, progression-free survival from Day 0 is a meaningful endpoint.

Disease-free survival was selected as the primary endpoint to demonstrate benefit in all patients with high grade disease who had failed prior BCG immunotherapy, with either CIS or papillary tumors, where cystectomy is generally advised. This endpoint facilitates estimating time to recurrence and, especially, progression to muscle-invasive disease.

Admittedly, because CIS patients are not disease-free at study entry, the interpretation of disease-free survival for these patients is not clear-cut. For this reason, patients with CIS tumors at study entry who did not achieve a disease-free state by Month 6 had their survival time set to 0 days. This approach admits that these patients were never disease-free and did not respond to treatment. Patients with CIS tumors at study entry who did achieve a disease-free state by Month 6 became “at risk” of recurrence from that point forward. Disease-free survival for these patients assumes the usual interpretation from Month 6 onward. For a patient with CIS, disease-free survival at 1 year indicates that the patient has been disease-free for at least 6 months.

Complete response is an alternative endpoint to measure treatment response in patients with CIS tumors. Recognizing this, estimates of complete response are presented in [Section 4.3.6](#). It should be noted that estimates of the disease-free survival rate equals the estimate of complete response proportion at 1 year if no patients are lost to follow up before 1 year. When patients are lost to follow-up, disease-free survival estimation censors those patients whereas the complete response approach must impute a response value; typically, the worst case is assumed and those patients lost to follow-up are assumed to be treatment non-responders.

## Statistical Methods

The primary analysis population included all patients who received at least 1 dose of MCNA (intent-to-treat [ITT]). A supportive population included only patients with high grade NMIBC per the central pathologist and who received at least 1 dose of MCNA (modified intent-to-treat [mITT]). In addition, a sensitivity analysis was based entirely on local pathology results.

The overall duration of disease-free survival, time to progression, and overall survival was calculated by the Kaplan-Meier technique, per protocol. Two-sided 95% confidence intervals were calculated using the log-log transformation estimate of the standard error.

The target of 40% disease-free survival at 1 year was based on minimal patient data (28 patients) using MCC Emulsion at 8 mg in Study 9708. We now recognize that the target of 40% was overly ambitious for several reasons. First, it did not take into account differences in response rates that could result from differences in baseline characteristics in the target population, such as tumor stage (CIS, Ta, or T1). Second, it did not factor in the implications of prior BCG induction courses and response (naïve, intolerant, relapsing, and refractory), and other risk factors not well documented at the time of study initiation. The populations in the Study 9708 (8 mg group) and Study 301 studies differ on prior BCG exposure and response, in addition to tumor stage. In addition, subjects with high grade papillary tumors were included only in the latter study. Taking into consideration a truly refractory target population, a disease-free survival rate of 40% at 1 year was overly ambitious; this has been recognized by many experts, including the FDA/AUA workshop panel ([Section 2.3](#)).

### 3.3 Study 303

Study 303 was designed and initiated as a randomized, active-controlled, open-label, multicenter study in patients with BCG refractory or BCG relapsing NMIBC. The study was initiated in November 2010, and the first patient was enrolled in February 2011. Out of the planned enrollment target of 450 patients and with 88 sites initiated, 84 patients were enrolled in 2 years: 29 in the first year and 55 in the second year of enrollment. Due to logistical problems, including slow recruitment, Study 303 was discontinued in November 2012. The decision to discontinue the study was based solely on logistical issues and was not due to any efficacy- or safety-related issues.

#### Objectives and Efficacy Endpoints

The primary objective of this study was to determine the efficacy of intravesical MCNA suspension as compared with mitomycin C. The primary efficacy variable was event-free survival, defined as the interval from randomization to documented tumor recurrence, tumor progression to muscle-invasive bladder cancer or death of any cause, whichever occurred first.

The secondary objective was to determine the safety of intravesical MCNA suspension as compared with mitomycin C.

Because final enrollment was < 20% of planned enrollment, the primary efficacy endpoint could not be evaluated. Selected efficacy results are summarized in [Section 13](#).

## Eligibility

For enrollment in Study 303, patients must have had BCG refractory or BCG relapsing NMIBC. BCG refractory disease was defined as evidence of persistent high grade bladder cancer at least 6 months from the start of a full induction course of BCG with or without maintenance/re-treatment at 3 months. BCG relapsing disease was defined as reappearance of disease after achieving a tumor-free status by 6 months following a full induction course of BCG with or without maintenance/re-treatment at 3 months. Patients with relapsing disease had to have relapsed within 18 months following the last dose of BCG. Patients must have had histologically confirmed NMIBC within 56 days prior to randomization, including high grade Ta papillary lesion(s), high or low grade T1 papillary lesion(s), or CIS, with or without Ta or T1 papillary tumor(s) of any grade. Patients must have had all visible papillary and resectable CIS lesion(s) removed by resection within 56 days prior to randomization and must have had an ECOG performance score of  $\leq 2$ . Patients with current or previous history of muscle-invasive bladder tumors were to be excluded from enrollment. A complete list of entry criteria is presented in [Section 11](#).

## Study Procedures and Dosing

The study was to be conducted over 3 years and was divided into 4 phases: Screening, Induction, Maintenance, and Follow-Up. The Screening Phase lasted up to 8 weeks, with a possible extension to 12 weeks if a re-resection was necessary. The Induction Phase consisted of the first 6 weeks of the study, during which time patients received weekly instillations of either MCNA suspension or mitomycin C. The Maintenance Phase lasted from Month 3 to Month 12. The Follow-Up Phase was to last a maximum of 24 months. The schedule of procedures is presented in [Section 12.2](#).

MCNA was administered intravesically at a dose of 8 mg reconstituted in a total of 50 mL of water for injection. The solution was to be retained in the bladder for at least 1 hour.

Safety assessments included adverse events, clinical laboratory values, vital signs, and physical examinations. Treatment-emergent adverse events were those events that started on or after the first instillation of the study medication and within 30 days after the last instillation of study medication. All patients were followed for adverse events for 30 days after their final study drug instillation.

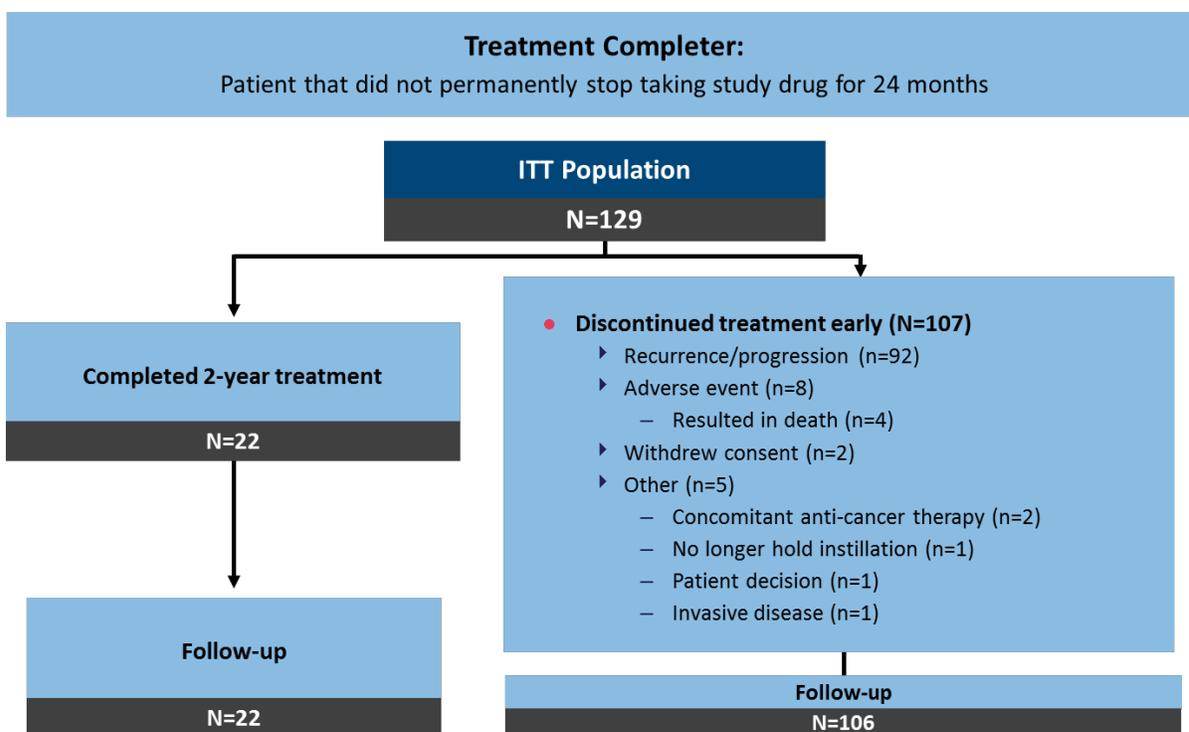
## 4 RESULTS FOR STUDY 301

### 4.1 Disposition

In Study 301, a total of 129 patients were treated with MCNA. Among the 129 treated patients, 22 patients (17.1%) completed the treatment of 2 years (Figure 9). The main reasons for terminating treatment early were tumor recurrence/progression (92 patients, 71.3%), adverse events (8 patients, 6.2%), other reasons (5 patients, 3.9%), and withdrawal by patient (2 patients, 1.6%).

Among the 129 treated patients, the mean duration of MCNA treatment was 270.8 days (Table 12).

**Figure 9. Disposition (Study 301)**



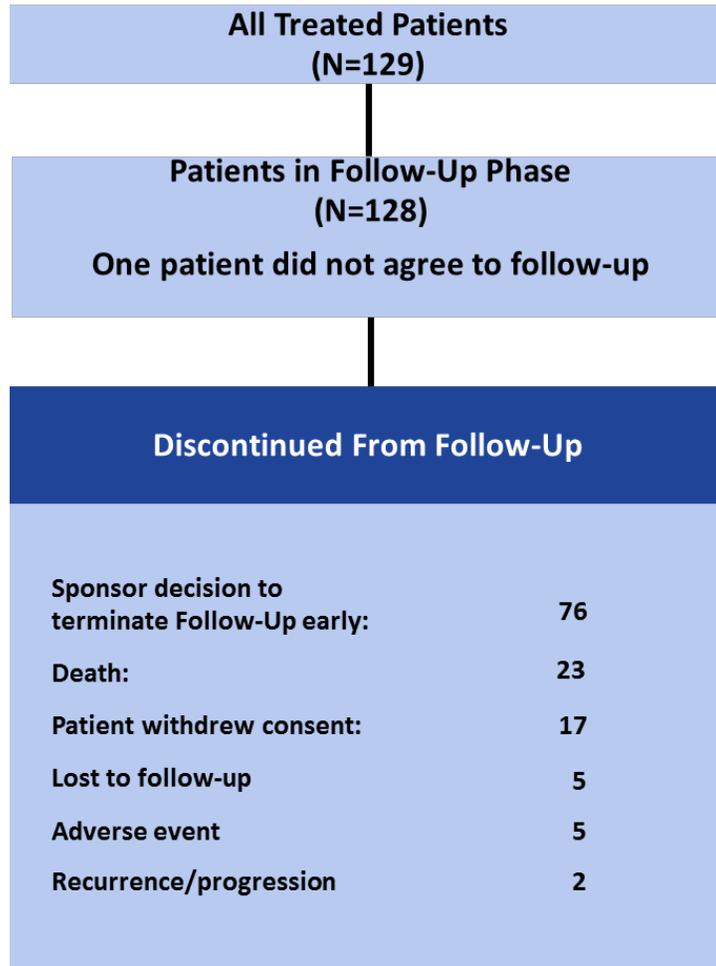
ITT = Intent-to-treat (included all patients who received at least 1 dose of the study drug)

The protocol for Study 301 stipulated that, if treatment was discontinued early, patients were asked to remain on the study with the remaining required evaluations in the Maintenance and Follow-Up Phases to be performed. All patients, except for 1 who withdrew consent, agreed to stay on the study for the follow-up (Figure 10).

Telesta stopped the Follow-Up Phase of Study 301 early since the primary and secondary efficacy endpoints, as well as safety endpoints, had already been determined. The median duration of follow-up from the time of the first dose of treatment to the last evaluation/contact, regardless of response to MCNA treatment, was 34.7 months for the 129 treated patients (range of 0.9 to 60.3 months).

With respect to the final disposition of the patients in the study, the most frequent reason (76 patients) for stopping study participation early was due to Telesta’s decision to stop the Follow-Up Phase of the study once the primary and secondary efficacy endpoints, as well as safety endpoints, had been determined. No patient completed the full 5-year planned duration of the study.

**Figure 10. Reasons for Patients Discontinuing Follow-Up Phase (Study 301)**



Note: The 4 patients who died while on treatment are considered as terminating the treatment AND study by their death. Although they never entered the Follow-Up Phase, these patients were counted as terminating the study due to an adverse event.

#### **4.2 Baseline Characteristics**

Among the 129 treated patients of Study 301, the median age of study patients was 71 years (range: 41 to 90 years) (Table 2). Most patients were male (95 patients; 73.6%) and all were white.

**Table 2. Demographic Baseline Characteristics (Study 301)**

<b>Baseline Characteristic Statistic</b>	<b>Study 301 MCNA (N = 129)</b>
Age (years)	
Mean (standard deviation)	68.5 (11.2)
Median	71.0
Minimum, maximum	41, 90
Gender, n (%)	
Male	95 (73.6)
Female	34 (26.4)
Race	
White	129 (100.0)
Black or African-American	0
Asian	0

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

According to the central pathologist in Study 301, 54 (41.9%) patients had CIS, 30 (23.3%) patients had a combination of CIS and papillary tumor(s) of any grade, 31 (24.0%) patients had papillary tumors only (of these 10, had low grade tumors), 7 (5.4%) patients had no tumor, and 2 (1.6%) patients had no results (Table 3). Within these 129 patients, 5 were determined to have muscle-invasive disease by the central pathologist.

**Table 3. Tumor Type (Study 301)**

<b>Central Pathologist Determination Tumor Type, n (%)</b>	<b>Study 301 MCNA (N = 129)</b>
CIS only	54 (41.9)
CIS and papillary tumors	30 (23.3)
Papillary only	31 (24.0)
Muscle-invasive disease	5 (3.9)
No tumor <sup>a</sup>	7 (5.4)
Unconfirmed <sup>b</sup>	2 (1.6)

CIS = carcinoma *in situ*; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

Note: Five patients with muscle-invasive disease based on the central pathologist's assessment had papillary only (3 patients) or CIS + papillary (2 patients) according to the local pathologist's assessment.

<sup>a</sup> Lack of tumor is due to a discrepancy between local and central pathologists. Three tumors were included as papillary only and 4 were included as CIS only for the primary analysis.

<sup>b</sup> Samples were lost or broken before they could be reviewed by the central pathologist. These tumors were included as CIS only for 1 patient, and as papillary only for 1 patient in the analysis of all treated patients.

In Study 301, all patients had received previous intravesical BCG therapy as required by the protocol; the median time from last BCG treatment to the first dose of MCNA was 204 days (range: 14 to 699 days); 206 days in BCG refractory subgroup and 190.5 days in BCG relapsing subgroup. A total of 45 (34.9%) patients had received previous intravesical chemotherapy; the majority 42 (93.3%) received mitomycin C.

### **4.3 Efficacy Results**

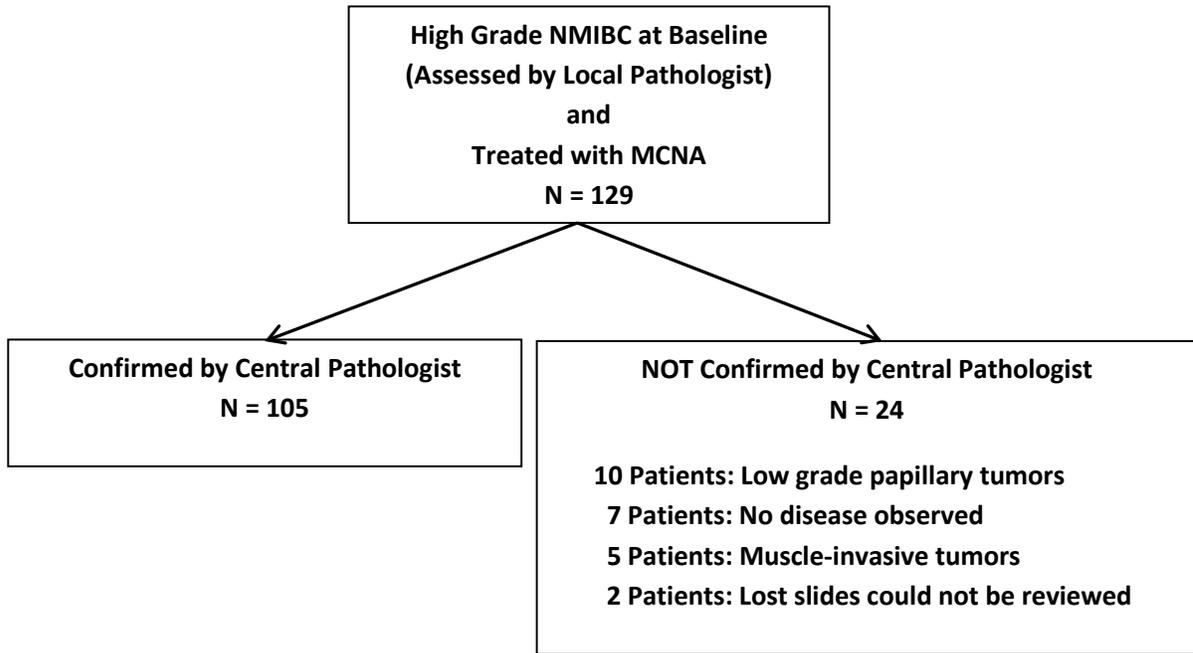
A total of 129 patients were treated with MCNA ([Figure 11](#)). Of the 129 treated patients, the central pathologist confirmed high grade NMIBC in 105 patients, although all 129 subjects had documented high grade disease when considered for study entry by the local pathologist. As a result of a discrepancy in diagnosis of high grade disease between the local and central pathologists, the slides/specimen were re-evaluated by the local pathologist. Following re-evaluation, the local pathologist changed the original high grade diagnosis to low grade in only 3 patients.

Efficacy summaries are based on all 129 patients treated with MCNA, unless stated otherwise. This approach is consistent with usual clinical practice, which is based on diagnoses from the local pathologists.

The efficacy endpoints of disease-free survival, complete response, and progression are based on assessments by the central pathologist in the primary efficacy analysis. The approach ensures consistent evaluation of biopsies during the study.

Sensitivity analyses were conducted on the basis of results from the local pathologist (at study entry and during the study). Note that patients could be discontinued from treatment for recurrence/progression on the basis of central pathology results, regardless of local pathology findings. Within these limitations, inferences based entirely on local pathology results are consistent with results based entirely on central pathology. Results for disease-free survival and complete response rates based entirely on local pathology are presented in [Section 14](#).

**Figure 11. Confirmation of High Grade NMIBC at Baseline by Local and Central Pathologists (Study 301)**



MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; NMIBC = non-muscle-invasive bladder cancer

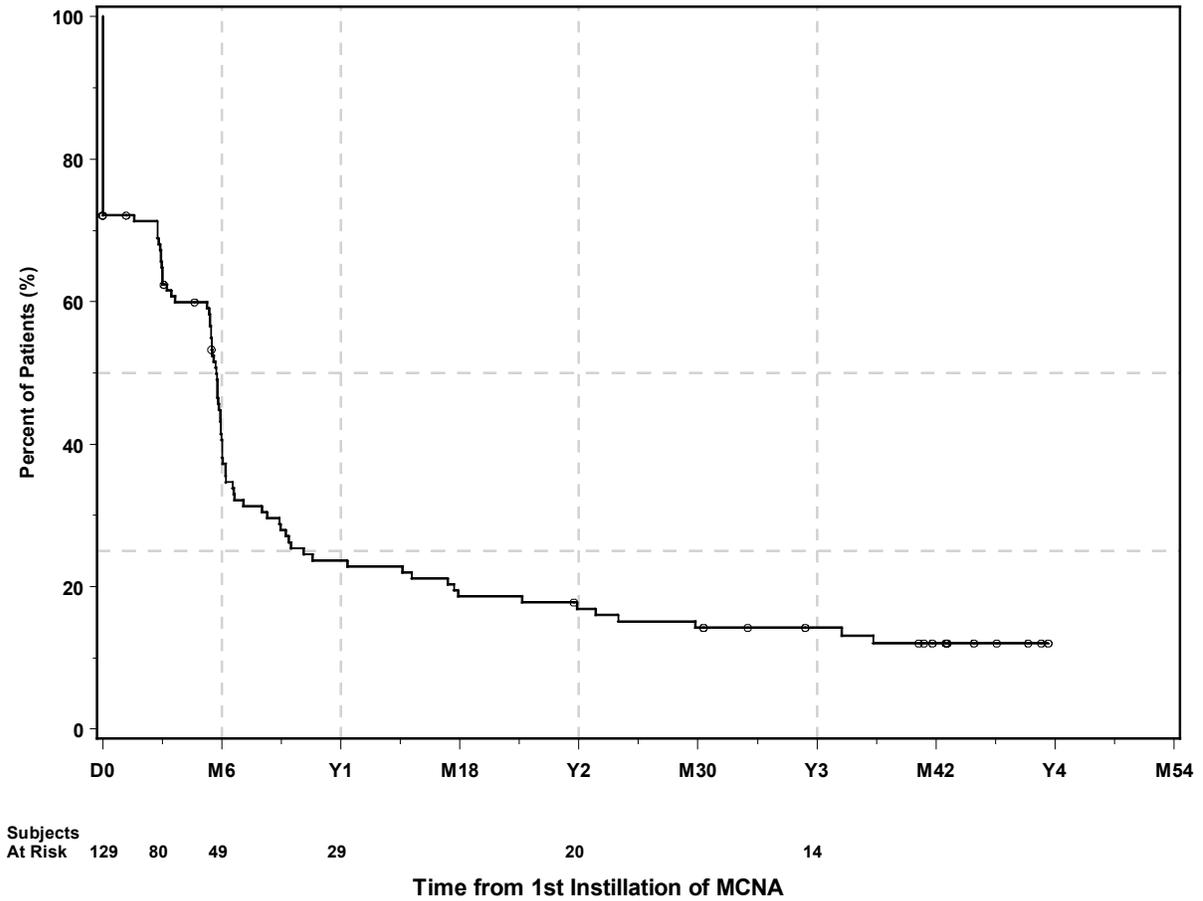
#### 4.3.1 Disease-Free Survival and Disease-Free Duration in All Patients

Disease-free survival of a patient was defined as the number of days from the first dose of MCNA to recurrence or progression or death, whichever came first; in the case of loss to follow-up, or withdrawal from the study, or study termination before any recurrence, progression, or death, the patient's disease-free survival was censored at the last tumor evaluation (latest of biopsy, cystoscopy, and urine cytology) or last tumor assessment before the start of other anti-cancer treatment, whichever was earlier. If there was any tumor (i.e., papillary tumor of any grade, presence of CIS, or muscle-invasive disease) at or after Month 6, the disease-free period ended the first time that disease was detected.

If there were papillary tumors only at Month 3, which persisted at Month 6, the disease-free period ended at Month 3, as the assumption was that the patients entered the study disease-free. In the case of CIS at study entry that did not disappear by Month 6, the disease-free period was defined as 0.

Based on the protocol-specified primary efficacy analysis, the disease-free survival rate at 1 year was 23.7% (95% confidence interval: 16.5% to 31.6%). The Kaplan-Meier disease-free survival curve for all treated patients is presented in [Figure 12](#).

**Figure 12. Kaplan-Meier Curve for Disease-Free Survival (Study 301, Intent-to-Treat)**

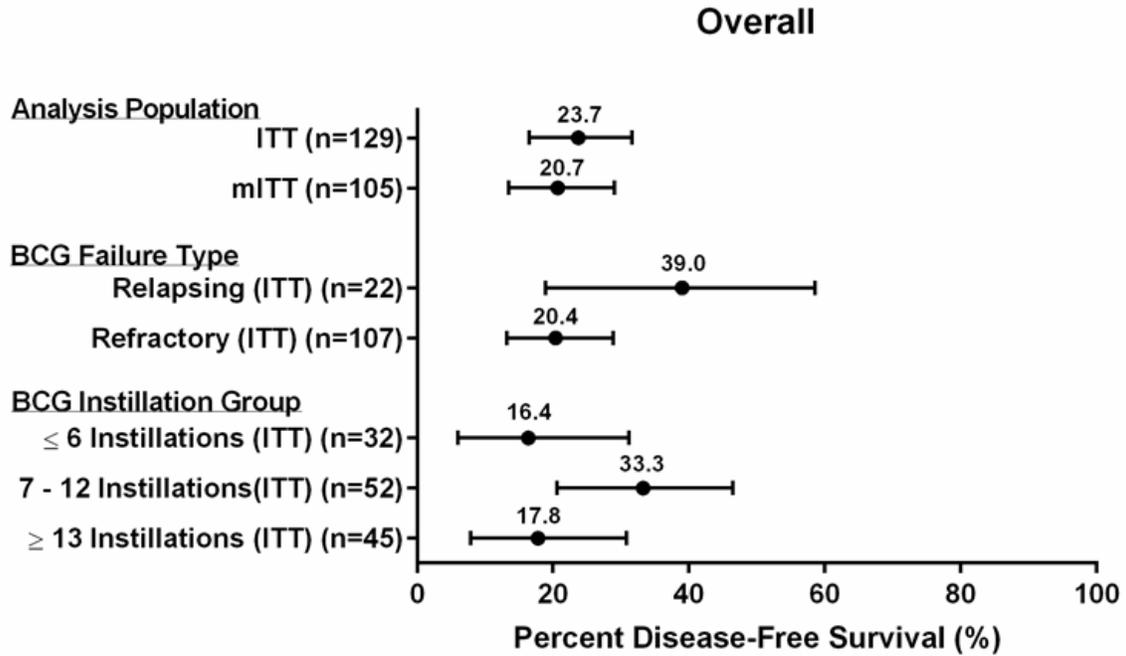


Censored observations are indicated by circles

D = day; M = month; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; Y = year

Figure 13 presents 95% confidence intervals for disease-free survival across analysis populations (ITT and mITT), type of BCG failure (relapsing and refractory), and number of BCG instillations ( $\leq 6$ , 7 to 12, and  $\geq 13$ ). The disease-free survival rate at 1 year was  $> 16\%$  for all groups. Tabular presentations of these analyses are provided in Section 15.

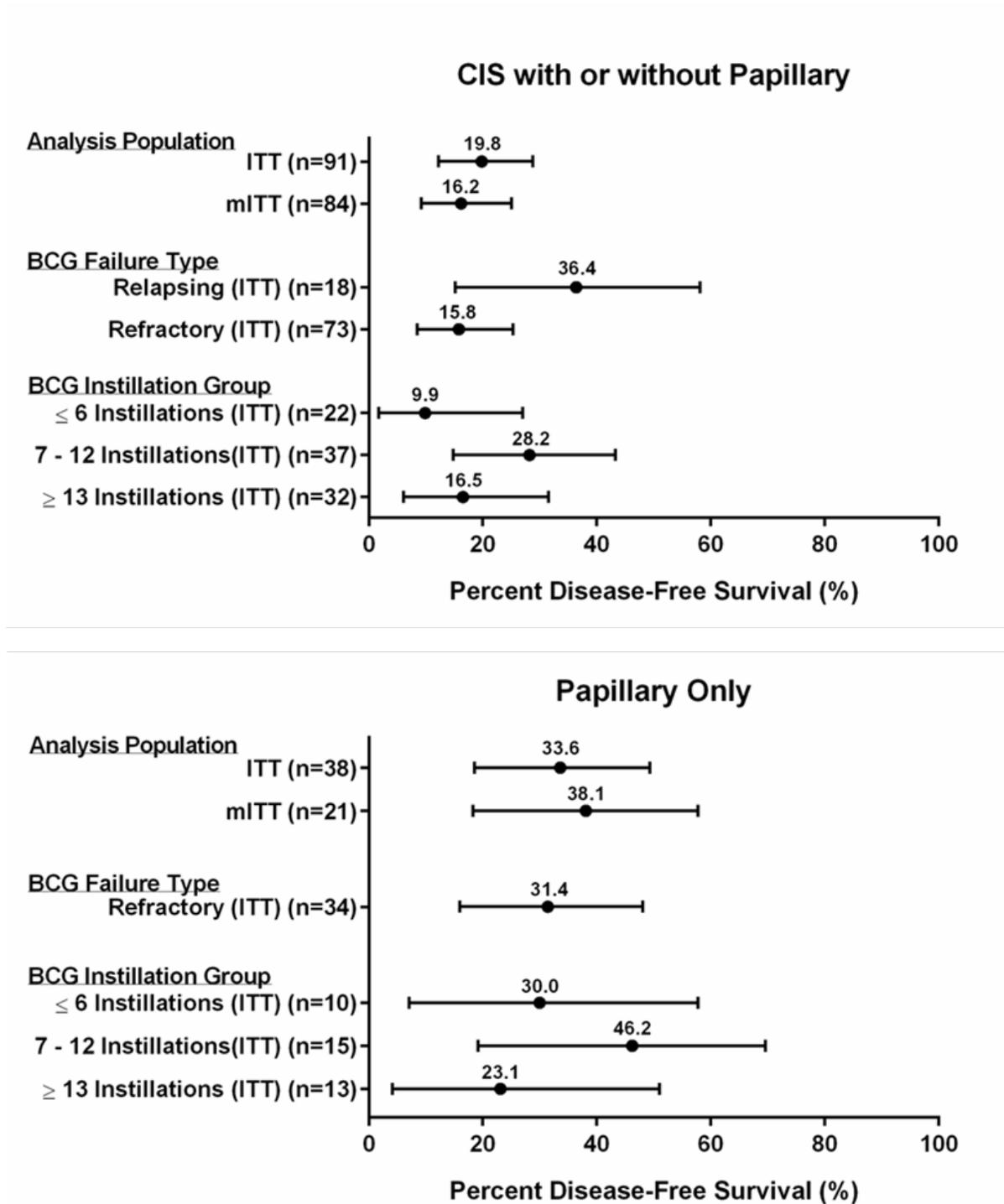
**Figure 13. Disease-Free Survival at 1 Year: 95% Confidence Intervals (Study 301)**



BCG = bacillus Calmette-Guérin; ITT = intent-to-treat; mITT = modified intent-to-treat

Figure 14 presents 95% confidence intervals for disease-free survival by baseline tumor type across analysis populations (ITT and mITT), type of BCG failure (relapsing and refractory), and number of BCG instillations ( $\leq 6$ , 7 to 12, and  $\geq 13$ ).

**Figure 14. Disease-Free Survival at 1 Year by Baseline Tumor Type: 95% Confidence Intervals (Study 301)**



BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat

### 4.3.2 Duration of Response for Patients Responding at 1 Year

The median duration of response for patients responding at 1 year is presented in Table 4. For the 28 responders at 1 year, the median duration of response was 34.0 months. Median duration of response varied across baseline tumor types from 26.0 months in patients with CIS with or without papillary tumors to 38.8 months in patients with papillary tumors only.

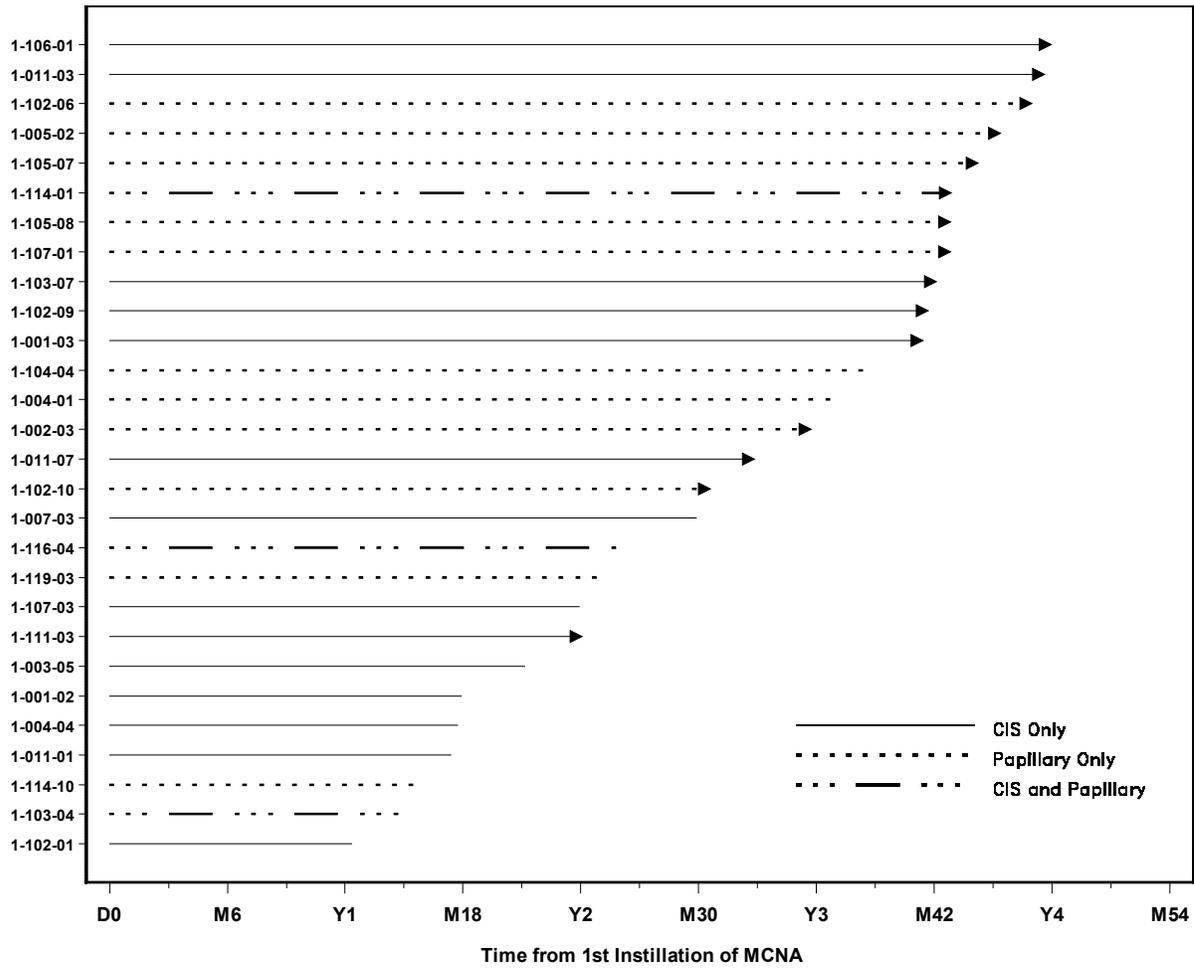
**Table 4. Duration of Response for Responders at 1 Year (Study 301)**

Population	Number of Patients	Arithmetic Median Duration of Response in Responders (Months)
Overall	28	34.0
CIS with or without papillary	17	26.0
CIS only	14	26.9
CIS and papillary	3	26.0
Papillary only	11	38.8

CIS = carcinoma *in situ*

Figure 15 depicts disease-free duration for the 28 patients responding to MCNA treatment at 1 year. The duration is from the first instillation of MCNA until the recurrence/progression or censoring date. For censored patients (those labeled with arrows), the last study day was the date of the last efficacy assessment or the last alive date. For 11 of the censored patients, the reason for censoring was due to early termination of the Follow-Up Phase. As a result, the disease-free duration shown in Figure 15 may be reflective of the minimum duration and may in fact have been longer if follow-up had been continued.

**Figure 15. Disease-Free Survival (Study 301, Intent-to-Treat Population, 1-Year Responders)**



CIS = carcinoma *in situ*; D = day; M = month; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; Y = year

Rate of response measured by disease-free survival at 1 year, number of responders at 1 year, and median duration of response in responders are presented in [Table 5](#) for the ITT population. The clinical response to MCNA was durable. At 1 year, approximately 1 out of 4 patients was alive and disease-free.

**Table 5. Rate of Response Measured by Disease-Free Survival at 1 Year, Number of Responders at 1 Year, and Median Duration of Response (Study 301, Intent-to-Treat Population)**

Population	Number of Patients	Disease-Free Survival at 1 Year (%)	Number of Responders at 1 Year	Arithmetic Median Duration of Response (Months)	Response Rate Based on 1-Year Disease-Free Survival Rate
Overall	129	23.7	28	34.0	1 out of 4
CIS ± papillary	91	19.8	17	26.0	1 out of 5
Papillary only	38	33.6	11	38.8	1 out of 3

CIS = carcinoma *in situ*

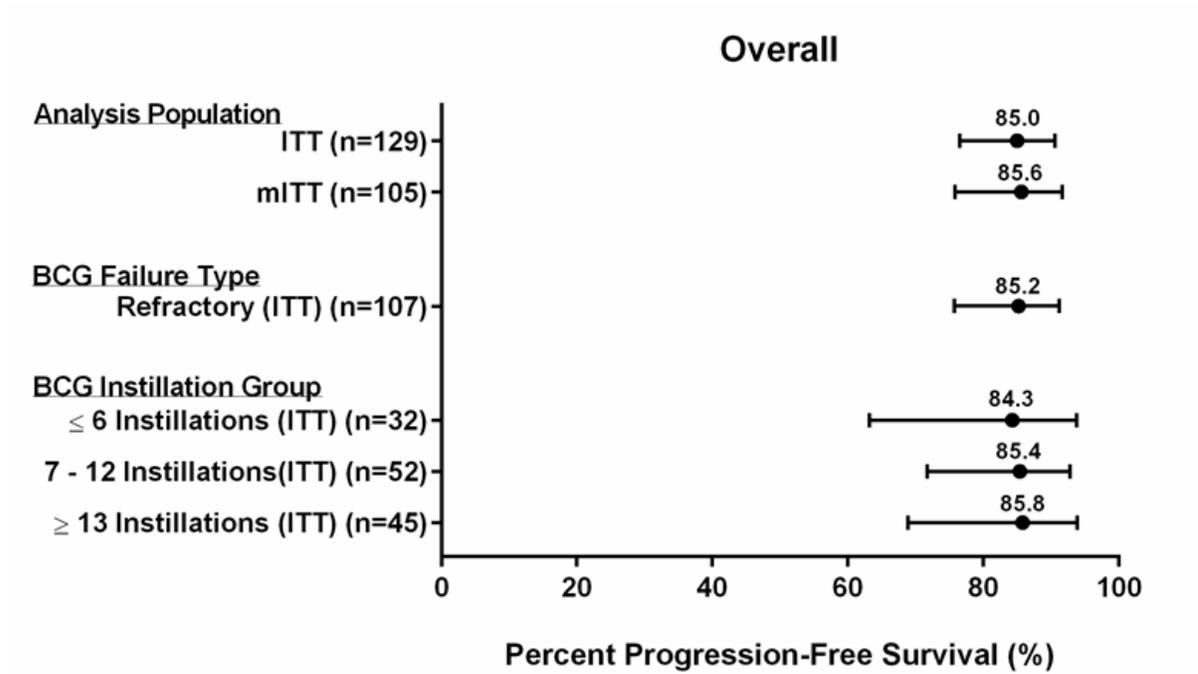
### 4.3.3 Progression-Free Survival for All Treated Patients

#### Progression-Free Survival at 1 Year

Patients with high-risk NMIBC are at high risk of progression to muscle-invasive disease, with an estimated 10 to 15% rate of progression per year [Sylvester 2002]. Thus, the top treatment priority is to prevent NMIBC from becoming muscle-invasive, which has a poor survival prognosis.

Figure 16 presents 95% confidence intervals for progression-free survival across analysis populations (ITT and mITT), type of BCG failure (refractory), and number of BCG instillations ( $\leq 6$ , 7 to 12, and  $\geq 13$ ). The progression-free survival rate at 1 year was high and similar across the groups. Tabular presentations of these results are provided in Section 16.

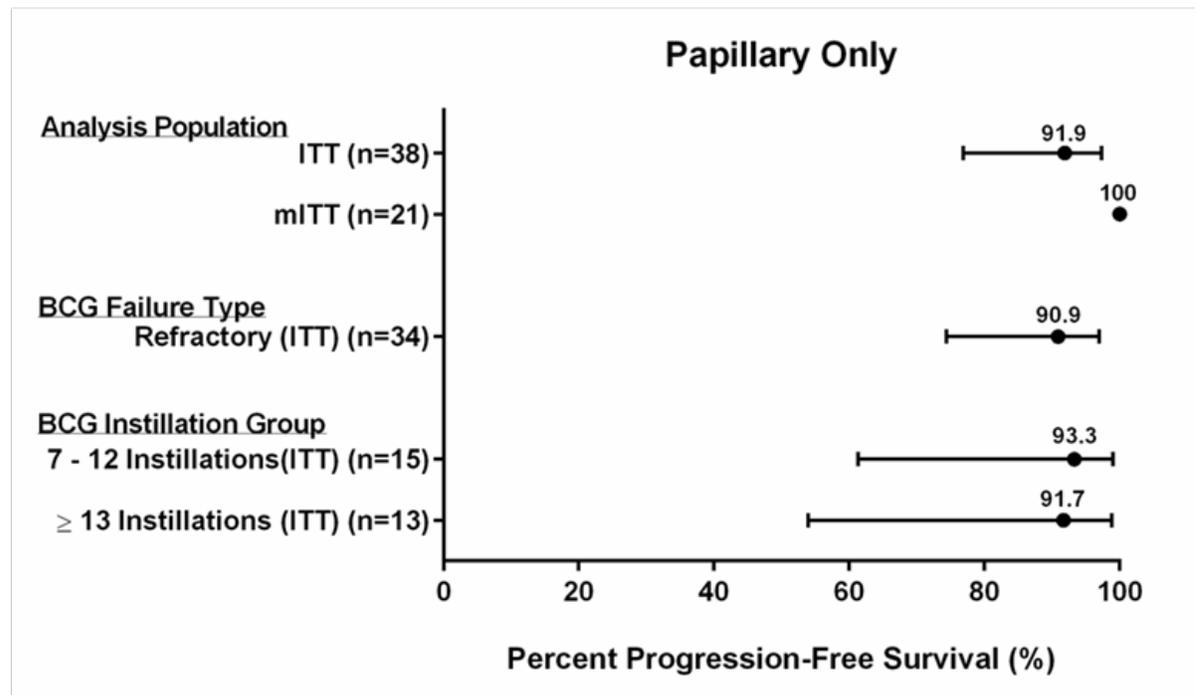
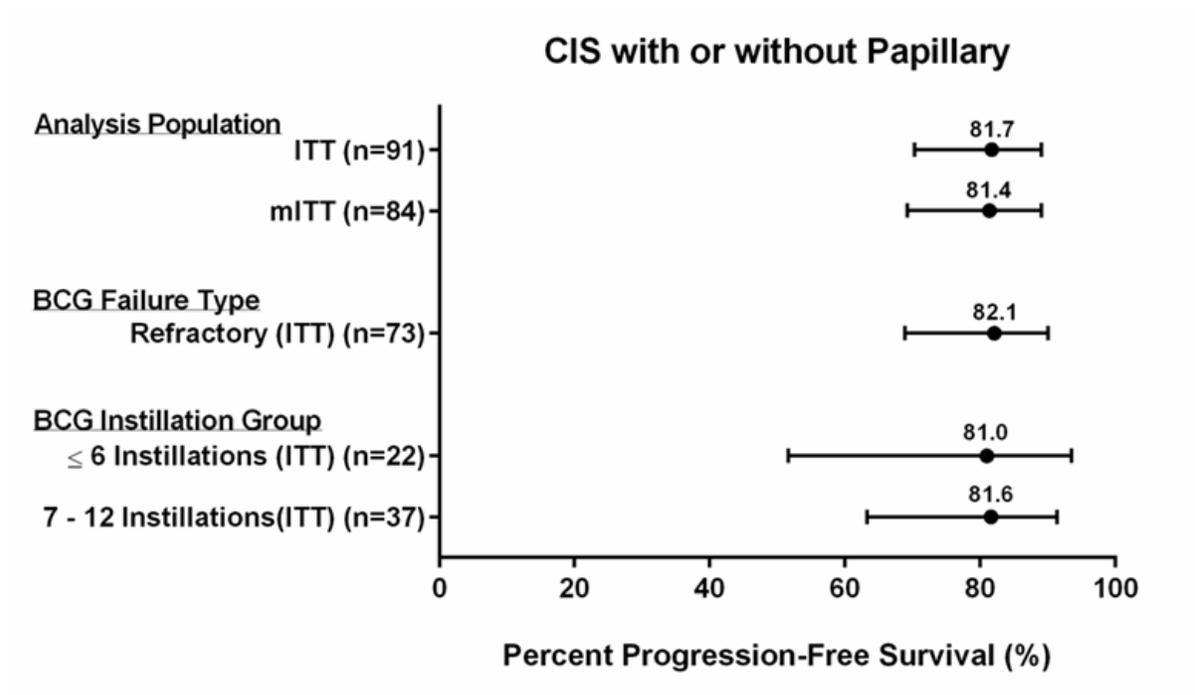
**Figure 16. Progression-Free Survival at 1 Year: 95% Confidence Intervals (Study 301)**



BCG = bacillus Calmette-Guérin; ITT = intent-to-treat; mITT = modified intent-to-treat

Figure 17 presents 95% confidence intervals for progression-free survival by baseline tumor type across analysis populations (ITT and mITT), type of BCG failure (refractory), and number of BCG instillations ( $\leq 6$ , 7 to 12, and  $\geq 13$ ). Within each baseline tumor type, the progression-free survival rate at 1 year was similar across groups.

**Figure 17. Progression-Free Survival by Baseline Tumor Type at 1 Year: 95% Confidence Intervals (Study 301)**



BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat  
Note: No confidence interval was calculated for the mITT population with papillary tumors at baseline because progression-free survival was 100%.

Among all treated patients, 31 experienced a progression event, categorized according to the most advanced event as organ confined progression (15 patients), metastatic bladder cancer (8 patients), or bladder cancer-related death (8 patients) during the Induction, Maintenance, and Follow-Up Phases of the study, and progression-free survival was based on these 31 patients. One patient with muscle-invasive disease at study entry discontinued treatment early due to an adverse event after receiving only 1 dose of MCNA. The patient had no pathological evaluations during study and was not counted in this population.

In the mITT population, 27 patients were considered to have a progression event, and progression-free survival was based on these 27 patients. Four of the 31 patients with a progression event already were diagnosed with muscle-invasive disease at study entry by the central pathologist. As a reminder, entry of patients with muscle-invasive disease occurred because the study entry eligibility for NMIBC was based on the local pathologist assessment. Those eligible as per the local pathologist were entered and received treatment and stayed on study, despite differences in diagnoses by the central pathologist.

Three of the 27 patients were responders at 1 year and their progression events were identified late (Day 972, 612, and 535 from start of treatment). The duration of response in these 3 responders at 1 year ranged between 1.5 and 2.7 years, and only 1 of the 3 responders had bladder removal.

### **Progression-Free Survival Across Time by 6-Month Response Status**

The progression-free survival rates of responders and non-responders were also estimated using a landmark analysis. The landmark time point of 6 months was chosen to assign patients as responders or non-responders because that was the first crucial time point to determine clinical response; patients continued or discontinued treatment at this time. Progression-free survival was estimated using cumulative incidence functions with exposure beginning at Month 6. Cumulative incidence functions are similar to the Kaplan-Meier method but account for competing risks. Patients who experienced progression or were lost to follow-up prior to Month 6 were excluded from the analysis.

The progression-free survival rate is presented by 6-month response in Table 6. Progression-free survival is markedly higher in patients who had responded at Month 6. Among patients who had not responded at Month 6, treatment did not increase progression beyond historical rates of about 10 to 15% per year [Sylvester 2002].

**Table 6. Progression-Free Survival Rate by 6-Month Response (Intent-to-Treat Population) (Study 301)**

Timepoint	Progression-Free Survival Rate (%)		
	Overall	6-Month Responders	6-Month Non-Responders
1 year	88.7	93.4	84.6
18 months	85.4	91.1	80.4
2 years	84.3	91.1	78.3
3 years	79.7	85.7	74.2

#### **4.3.4 Bladder Removal**

A total of 55 (43%) patients underwent bladder removal during the study ([Table 7](#)). Median time to bladder removal was 263 days from the first instillation of MCNA. Among patients for whom MCNA failed, median time from MCNA treatment failure to bladder removal was 173.5 days.

The rate of bladder removal among patients with complete response at 1 year was 17.9% (5 out of 28 patients), in comparison to 49.5% (50 out of 101 patients) among patients who did not have complete response at 1 year.

Among those 55 patients, 17 had stage T2 or higher disease. Five of the 55 patients were disease-free at 1 year.

Within the 55 patients who had cystectomy, 13 (24%) received additional intravesical therapy between MCNA failure and the subsequent cystectomy, compared to the non-cystectomy group in which 34 (46%) of 74 patients received intravesical therapy after MCNA failure.

**Table 7. Tumor Status at Bladder Removal (Study 301)**

	Baseline Tumor Type			Total
	CIS Only	CIS and Papillary	Papillary Only	
ITT Population	n=29	n=16	n=10	n=55
Bladder removal surgery (days after first dose)				
Median	253.0	241.0	381.0	263.0
Minimum, maximum	112, 1227	109, 1227	114, 933	109, 1227
CIS at bladder removal, n (%)				
No	3 (10.3)	2 (12.5)	5 (50.0)	10 (18.2)
Yes	26 (89.7)	14 (87.5)	5 (50.0)	45 (81.8)
Papillary tumor stage at bladder removal, n (%)				
Ta	3 (10.3)	1 (6.3)	3 (30.0)	7 (12.7)
T1	2 (6.9)	2 (12.5)	3 (30.0)	7 (12.7)
<b>T2-4 (muscle-invasive)</b>	<b>9 (31.0)</b>	<b>5 (31.3)</b>	<b>3 (30.0)</b>	<b>17 (30.9)</b>
Not applicable	15 (51.7)	8 (50.0)	1 (10.0)	24 (43.6)
Tumor grade at bladder removal, n (%) <sup>a</sup>				
Number of tumors	n=23	n=13	n=9	n=45
High	22 (95.7)	13 (100.0)	8 (88.9)	43 (95.6)
Low	1 (4.3)	0	1 (11.1)	2 (4.4)
mITT Population	n=29	n=15	n=8	n=52
Bladder removal surgery (days after first dose)				
Median	253.0	243.0	507.0	276.0
Minimum, maximum	112, 1227	109, 1227	205, 933	109, 1227
CIS at bladder removal, n (%)				
No	3 (10.3)	1 (6.7)	3 (37.5)	7 (13.5)
Yes	26 (89.7)	14 (93.3)	5 (62.5)	45 (86.5)
Papillary tumor stage at bladder removal, n (%)				
Ta	3 (10.3)	1 (6.7)	2 (25.0)	6 (11.5)
T1	2 (6.9)	2 (13.3)	3 (37.5)	7 (13.5)
<b>T2-4 (muscle-invasive)</b>	<b>9 (31.0)</b>	<b>4 (26.7)</b>	<b>2 (25.0)</b>	<b>15 (28.8)</b>
Not applicable	15 (51.7)	8 (53.3)	1 (12.5)	24 (46.2)
Tumor grade at bladder removal, n (%) <sup>a</sup>				
Number of tumors	n=23	n=12	n=7	n=42
High	22 (95.7)	12 (100.0)	7 (100.0)	41 (97.6)
Low	1 (4.3)	0	0	1 (2.4)

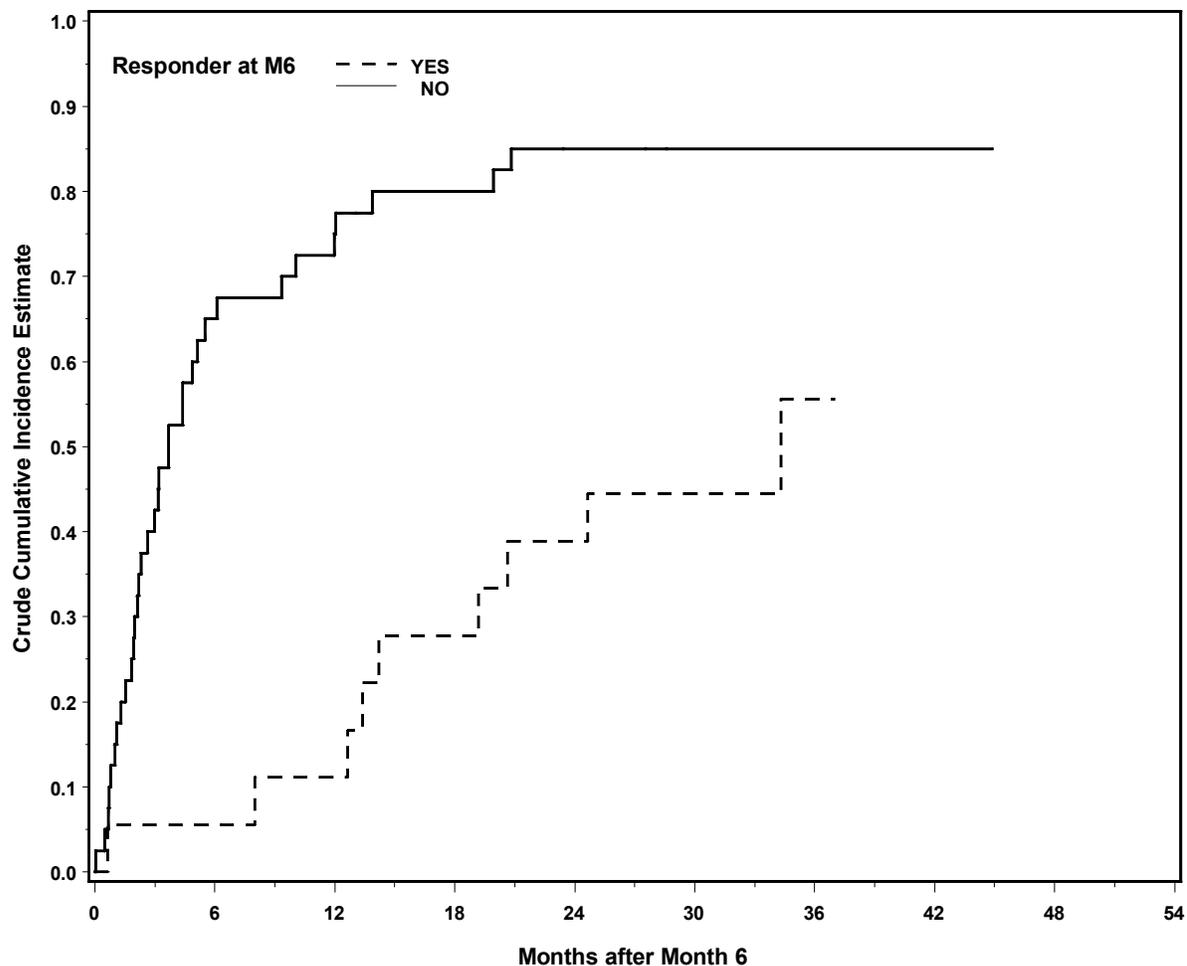
CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat

Note: Tumor stage is based on the central pathologist's assessment.

<sup>a</sup> Tumor grade at bladder removal was based on the total number of responses rather than the total number of patients in the ITT and mITT populations.

Similar to the landmark analysis of progression-free survival, the rates of bladder removal for Month 6 responders compared to non-responders were estimated using cumulative incidence functions (Figure 18). The rate of bladder removals was much higher in the non-responder group; at 6 months after the landmark time, the rates were 5.6% for responders and 65.0% for non-responders, and at 12 months, 11.1% for responders and 75% for non-responders.

**Figure 18. Cumulative Incidence of Cystectomy in Responders and Non-Responders (Study 301)**

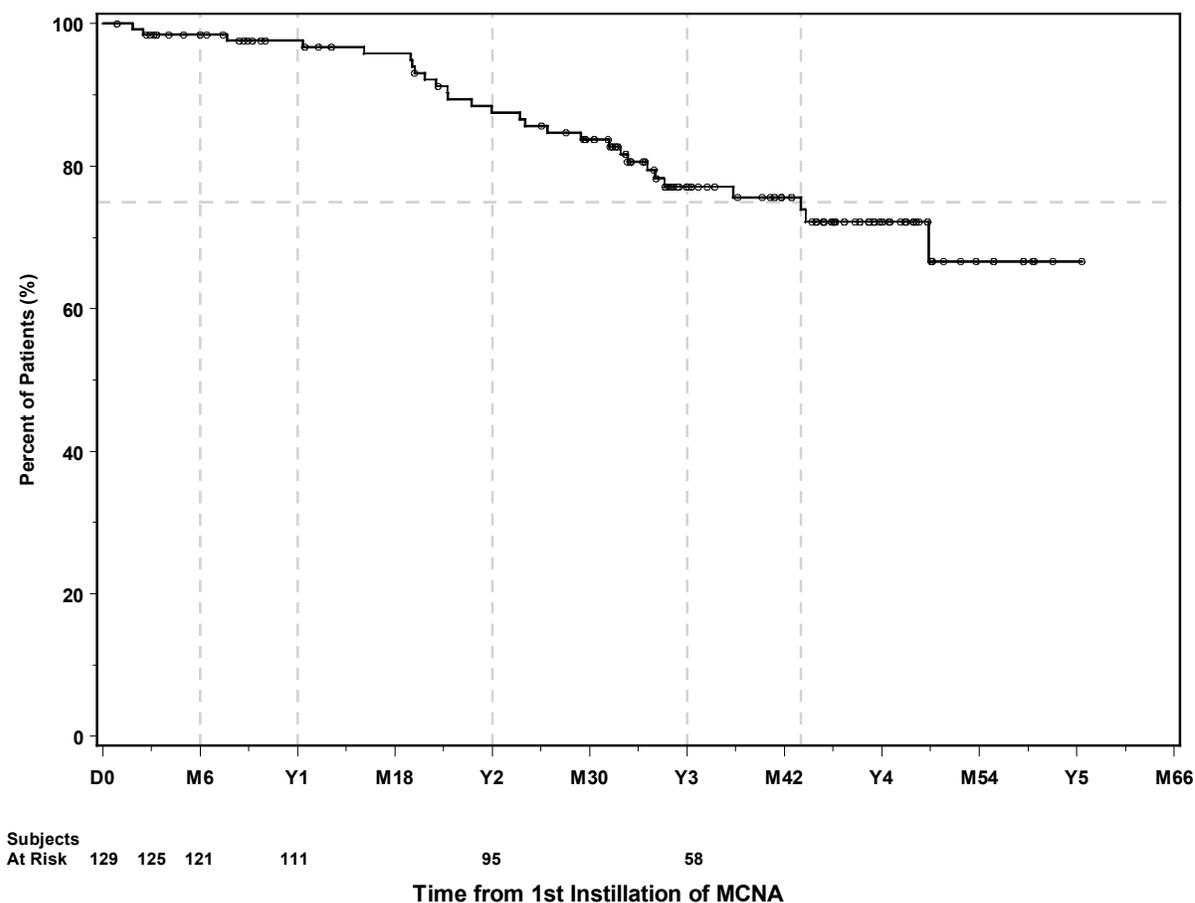


M6 = Month 6

#### 4.3.5 Overall Survival

A total of 28 (21.7%) patients died. The overall survival rate at 3.5 years, estimated using the Kaplan-Meier method, was 75%. Median survival could not be estimated because fewer than 50% of patients died. Four of the deaths occurred during the treatment phase (Induction/Maintenance), 23 occurred during the Follow-Up Phase, and 1 occurred after the patient's end-of-study visit. Kaplan-Meier survival estimates are presented in Figure 19. A listing of patients who died, including the primary cause of death, is provided in Section 17.

**Figure 19. Overall Survival Time (Study 301, Intent-to-Treat)**



Censored observations are indicated by circles

D = day; M = month; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; Y = year

#### 4.3.6 Complete Response for Patients with CIS Tumors

Because CIS tumors are not resected at baseline, patients with these tumors are not disease-free at the start of treatment and complete response, rather than disease-free survival, is considered to be a more appropriate measure of efficacy. This approach is reinforced by the FDA/AUA workshop panel (Section 2.3). If patients are lost to follow-up, the Kaplan-Meier approach censors those lost to follow-up, whereas complete response must impute a response status at the assessment. However, patients with only papillary tumors at baseline had all their tumors resected, and strictly speaking, were disease-free before treatment with MCNA.

Complete response was defined as the absence of a positive biopsy (the same definition used for disease-free) and was estimated by calculating a proportion in which observations censored prior to the time-point of interest were treated as non-responders or treatment failures.

Among all treated patients with CIS with or without papillary tumors, the complete response rate was 36.3% at Month 6, 18.7% at Month 12, and 9.9% at Month 24 (Table 8). A breakdown of the patients with a CIS component into CIS only and CIS with papillary tumors showed a higher complete response rate for patients with only CIS tumors.

**Table 8. Complete Response Rate Over Time in Patients with CIS (Study 301)**

Analysis Population Tumor Type at Baseline	N	Number (%) Subjects with Complete Response		
		6 Months	12 Months	24 Months
ITT Population				
CIS with or without papillary	91	33 (36.3)	17 (18.7)	9 (9.9)
CIS only	59	26 (44.1)	14 (23.7)	7 (11.9)
CIS with papillary tumors	32	7 (21.9)	3 (9.4)	2 (6.3)
mITT Population				
CIS with or without papillary	84	27 (32.1)	13 (15.5)	7 (8.3)
CIS only	54	21 (38.9)	10 (18.5)	5 (9.3)
CIS with papillary tumors	30	6 (20.0)	3 (10.0)	2 (6.7)

CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat

Among all treated patients with CIS with or without papillary tumors, the complete response rate was higher for BCG relapsing patients as compared to BCG refractory patients (Table 9).

**Table 9. Complete Response Rate Over Time by BCG Failure Type (Study 301)**

	N	Number (%) Subjects with Complete Response		
		6 Months	12 Months	24 Months
ITT Population – BCG Relapsing				
CIS with or without papillary	18	8 (44.4)	6 (33.3)	5 (27.8)
CIS only	11	6 (54.5)	5 (45.5)	4 (36.4)
CIS with papillary tumors	7	2 (28.6)	1 (14.3)	1 (14.3)
ITT Population – BCG Refractory				
CIS with or without papillary	73	25 (34.2)	11 (15.1)	4 (5.5)
CIS only	48	20 (41.7)	9 (18.8)	3 (6.3)
CIS with papillary tumors	25	5 (20.0)	2 (8.0)	1 (4.0)
mITT Population – BCG Relapsing				
CIS with or without papillary	18	8 (44.4)	6 (33.3)	5 (27.8)
CIS only	11	6 (54.5)	5 (45.5)	4 (36.4)
CIS with papillary tumors	7	2 (28.6)	1 (14.3)	1 (14.3)
mITT Population – BCG Refractory				
CIS with or without papillary	66	19 (28.8)	7 (10.6)	2 (3.0)
CIS only	43	15 (34.9)	5 (11.6)	1 (2.3)
CIS with papillary tumors	23	4 (17.4)	2 (8.7)	1 (4.3)

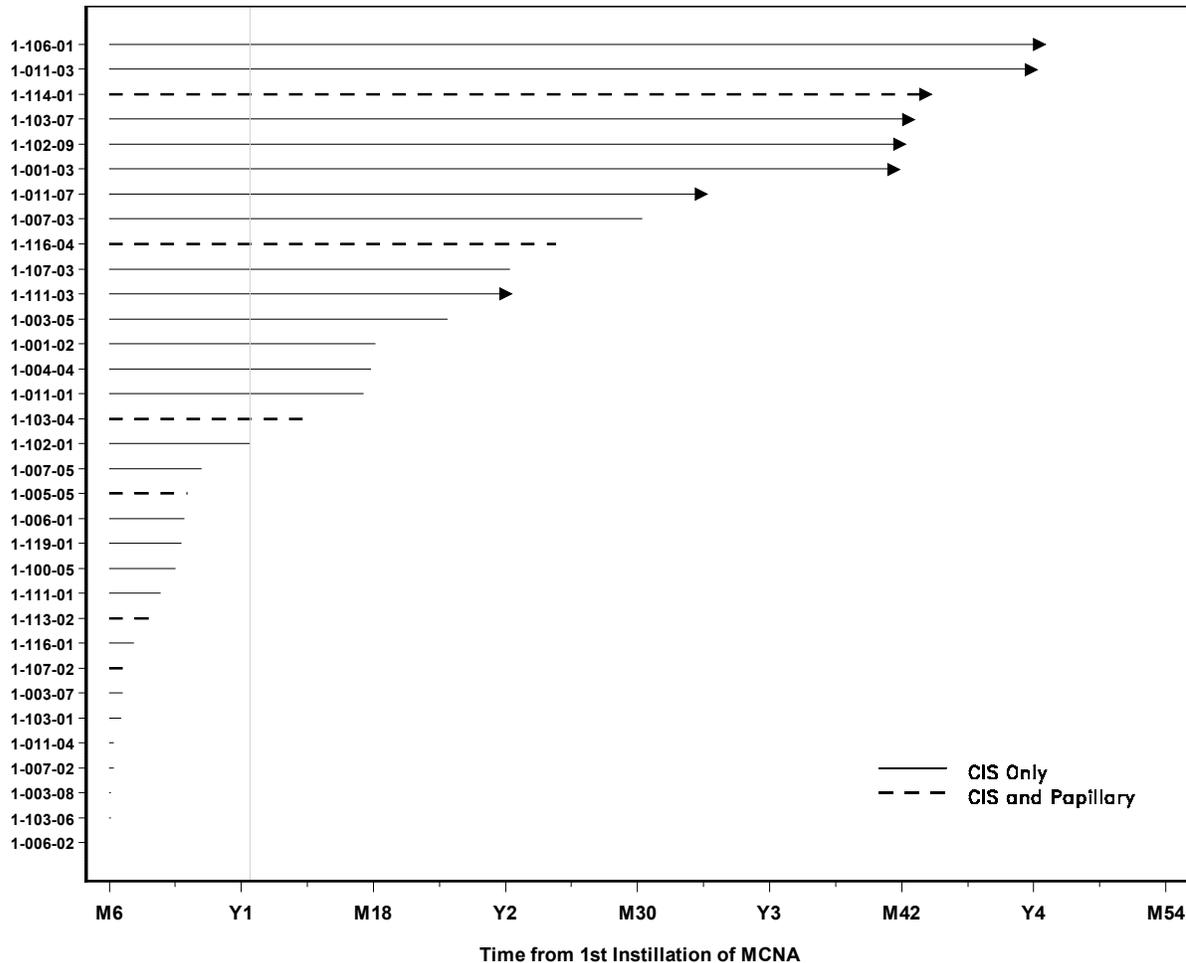
BCG = bacillus Calmette-Guérin; CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat

Figure 20 demonstrates the duration of complete response for the 33 patients with CIS with or without papillary tumors at baseline who responded to MCNA treatment at Month 6. The

duration of response is from the first instillation of MCNA until the recurrence/progression or censoring date. For censored patients (those labeled with arrows), the last study day was the date of the last efficacy assessment or the last alive date.

For 6 of the censored patients, the reason for censoring was due to the early termination of the Follow-Up Phase. As a result, the duration of response shown in Figure 20 may be reflective of the minimum duration and may in fact have been longer if follow-up had been continued.

**Figure 20. Duration of Response After Month 6 (Study 301, Intent-to-Treat, 6-Month Responders with CIS at Baseline)**



CIS = carcinoma *in situ*; M = month; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; Y = year

#### 4.3.7 Comparison of Complete Response in Study 301 to Valrubicin

The open-label, non-comparative study that supported approval of valrubicin by the FDA was used to provide an external benchmark for MCNA [Steinberg 2000]. The complete response rate for valrubicin at Month 6 was calculated from 90 patients with BCG refractory CIS disease who received at least 2 prior courses of intravesical therapy (1 of which was BCG). Each patient received 6 weekly intravesical administrations of valrubicin and complete response was documented by bladder biopsy and cytology at Month 6. The

majority of patients were male (88%), white (98%), and  $\geq 60$  years of age (mean of 68 years). All patients had tried  $\geq 2$  courses of intravesical therapy, and 70% had received  $\geq 2$  courses of BCG. The mean number of previous resections was 5.0. In the 17 patients with CIS and concurrent papillary disease, most papillary tumors were of grade 2 or higher.

Valrubicin resulted in an 18.0% (16/90) complete response rate at 6 months. Recurrence was noted in 79 patients, including only 2 patients with clinically advanced disease (stage T2). Of these 79 patients, 44 (56%, 4 responders and 40 non-responders) underwent bladder removal.

In a supportive open-label study, BCG refractory/relapsing/intolerant adults with CIS disease ( $\geq 1$  previous course of BCG or could not complete a BCG course owing to toxicity or contraindication) were randomized to receive 6 or 9 weekly intravesical valrubicin (800 mg) instillations [Dinney 2013]. The majority of patients were male (84%), white (93%), and  $\geq 60$  years of age (mean of 70 years). Most patients had tried  $\geq 1$  course of intravesical therapy, and 39% had received  $\geq 2$  courses of BCG. The mean number of previous resections was 3.2. In patients with CIS and concurrent papillary disease, most papillary tumors were of grade 3 or 4 (13/18 patients).

For the 80 treated patients in that supportive study, the complete response rate was 18%. Kaplan-Meier analysis indicated a probability of disease-free status of 22% at 6 months. Overall, 25% of patients underwent bladder removal, including 17 of 50 patients (34%) who did not respond. The probability of bladder removal was 12% at 6 months, 24% at 1 year, and 30% at 2 years.

In summary, the complete response rate for valrubicin at 6 months was 18.0% in the pivotal study and 56% of patients underwent bladder removal. In comparison, the complete response rate at 6 months for MCNA in Study 301 was 36.3% for patients with CIS with or without papillary tumors. A total of 55 (43%) patients underwent bladder removal during Study 301; among these, 45 patients had CIS with or without papillary tumors at baseline.

#### **4.4 Discussion and Conclusion for Study 301**

Approximately 24% of the treated patients were disease-free at 1 year. Among patients who were disease-free at this time point, the response to MCNA was durable and lasted almost 3 years. In addition, patients treated with MCNA were not placed at greater risk of progression, bladder removal, or death; most importantly, patients were provided a potentially bladder-preserving treatment without undue risk from a delay in surgery.

Evidence for these conclusions includes:

- Among all 28 responders at 1 year, the median duration of response was 34.0 months.
- Progression-free survival at 1 year was 85.0% among all treated patients; this is consistent with historical reports for high risk NMIBC.
- For responders at Month 6, the progression-free survival rate was 85.7% at 3 years. For non-responders at Month 6, the progression-free survival rate was 74.2% at 3 years. Note that this analysis excludes patients who discontinued the study or experienced progression before Month 6.
- The bladder was preserved for most patients.

- A total of 55 out of 129 patients underwent bladder removal over the study period, with a median time to bladder removal of 263 days from the first instillation of MCNA. Among patients for whom MCNA failed, median time from MCNA treatment failure to bladder removal was 173.5 days.
- The rate of bladder removal among patients who responded to MCNA at 1 year was 17.9% (5 out of 28 patients), compared to 49.5% (50 out of 101 patients) among patients who did not respond to MCNA at 1 year.
- Among the 55 patients, 17 had muscle-invasive or metastatic disease at time of bladder removal.
- Within the 55 patients who underwent cystectomy, 13 (24%) received additional intravesical therapy between MCNA failure and the subsequent cystectomy, compared to the non-cystectomy group in which 34 (46%) of 74 patients received intravesical therapy after MCNA failure.
- Results for subpopulations based on specific baseline characteristics include:
  - Among all treated patients with CIS with or without papillary tumors, the complete response rate at 1 year was 18.7%. The complete response rate was 15.1% and 33.3% for the BCG refractory and BCG relapsing populations, respectively. Among the 17 responders with CIS, the median duration of response was 26.0 months.
  - Among all treated patients with papillary tumors only, the disease-free survival rate at 1 year was 33.6%. Among the 11 responders with papillary tumors only who were disease free at 1 year, the median duration of response was 38.8 months.

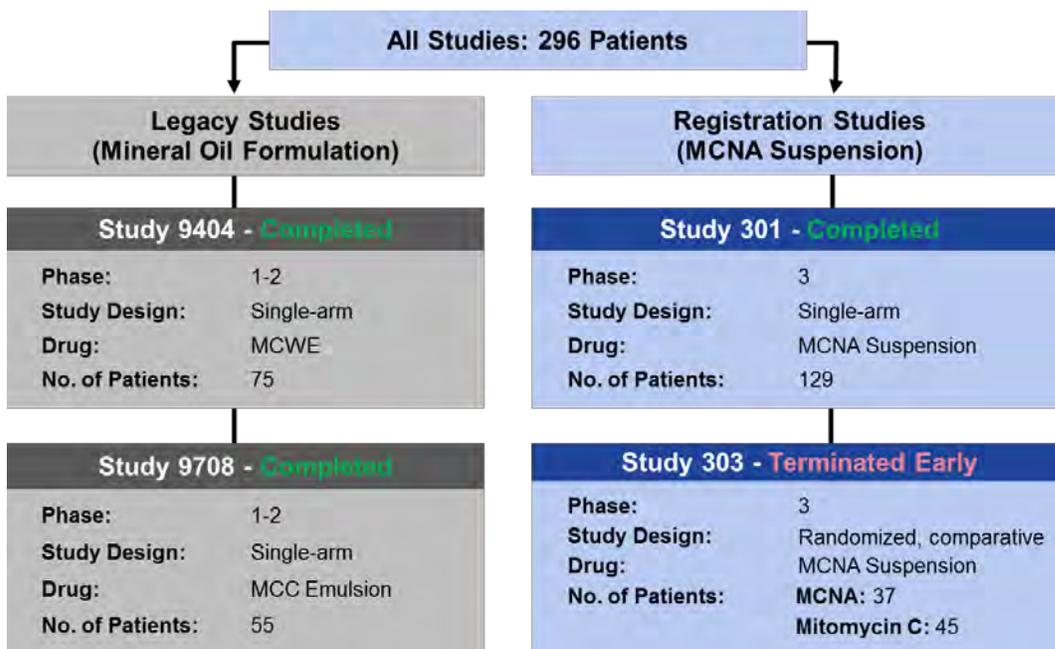
## 5 SAFETY DATA

Throughout the clinical development program, safety was evaluated through the collection of adverse events and assessment by the investigator of their intensity, relationship to treatment, onset, duration, and outcome. All adverse events, including serious adverse events, changes in physical examinations, laboratory values and other observations related to safety, were monitored and recorded.

### 5.1 Overview of Safety Evaluation

A total of 296 patients were treated with 1 of the 3 formulations derived from *Mycobacterium phlei* (Figure 21).

**Figure 21. Number of Patients Exposed to Mycobacterium Cell Wall Compositions in Prospective Clinical Studies**



DNA = deoxyribonucleic acid; MCC = Mycobacterial Cell Wall-DNA Complex; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; MCWE = Mycobacterial Cell Wall Extract

The safety evaluation is based on the data generated in a total of 166 patients recruited and treated with MCNA in Phase 3 Studies 301 and 303, as both trials have used the same mycobacterial cell wall composition, MCNA Suspension, which is the formulation to be marketed.

MCNA for intravesical administration was supplied as a suspension in water for injection at a concentration of 1.0 mg/mL and the dose administered in both studies was 8 mg. A total of 8 mL of MCNA was diluted in 42 mL of water for injection, for a total instillate volume of 50 mL. Dose adjustments were not allowed.

The primary analysis of safety for MCNA is based on Study 301 where 129 patients were treated for a period of up to 2 years, whereas only 37 patients received MCNA for a period of up to 1 year in the early-terminated Study 303.

The data from the 2 legacy proof-of-concept studies were not used to support the safety component of this application due to differences in formulations, treatment exposure and disease characteristics.

In Studies 301 and 303, the safety population was defined as all patients who received at least 1 dose of study medication. Patients who were not treated with study drug are excluded from the safety population.

Treatment-emergent adverse events include all adverse events that began between the first administration of study treatment up to 30 days after the last administration of study treatment for Study 303, and up to 35 days for Study 301.

The causal relationship of adverse events to study treatment was assessed by the clinical investigators and was categorized as possibly, probably, or definitely related.

## **5.2 Disposition**

In Study 301, a total of 129 patients were treated with MCNA. Among the 129 treated patients, 22 patients (17.1%) completed the treatment of 2 years ([Table 10](#)). The main reasons for terminating treatment early were tumor recurrence/progression (92 patients, 71.3%), adverse events (8 patients, 6.2%), other reasons (5 patients, 3.9%), and withdrawal by patient (2 patients, 1.6%).

In Study 303, a total of 84 patients were randomized (39 patients in the MCNA arm and 45 patients in the mitomycin C arm); 37 patients were treated with MCNA, and 45 patients were treated with mitomycin C. Six patients completed all study treatments (2 patients treated with MCNA; 4 patients treated with mitomycin C), but no patient completed the study because it was terminated due to slow recruitment. The most frequent reason for discontinuation from treatment in the MCNA arm was tumor recurrence/progression (18 patients, 48.6%).

**Table 10. Disposition (Study 301 and Study 303)**

Disposition, n (%)	Study 301	Study 303	
	MCNA (N = 129)	MCNA (N = 39)	Mitomycin C (N = 45)
Randomized	No randomization	39	45
Treated	129	37	45
Completed treatment	22 (17.1)	2 (5.4)	4 (8.9)
Discontinued from Treatment			
Withdrawal by patient	2 (1.6)	0	2 (4.4)
Patient non-compliance	0	0	1 (2.2)
Physician decision	NA	3 (8.1)	3 (6.7)
Sponsor decision	NA	2 (5.4)	6 (13.3)
Tumor recurrence/progression	92 (71.3)	18 (48.6)	10 (22.2)
Adverse event	8 (6.2)	1 (2.7)	0
Other	5 (3.9)	11 (29.7)	18 (40.0)
Discontinued from Study	(N = 128) <sup>a</sup>		
Death	23 (18.0)	0	0
Protocol violation	0	1 (2.6)	0
Withdrawal by patient	17 (13.3)	2 (5.1)	4 (8.9)
Lost to follow-up	5 (3.9)	0	0
Tumor recurrence/progression	2 (1.6)	9 (23.1)	10 (22.2)
Adverse event	5 (3.9)	0	0
Other	76 (59.4) <sup>b</sup>	27 (69.2)	31 (68.9)

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; NA = not an available option on the case report form

<sup>a</sup> One patient did not agree to participate in the Follow-Up Phase and percentages are based on denominator of 128.

<sup>b</sup> Sponsor decision to terminate the study Follow-Up Phase early (prior to Month 60).

### 5.3 Exposure

The induction regimen for MCNA consisted of 6 weekly instillations in both Study 301 and Study 303. The maintenance regimen differed between studies and consisted of 3 weekly instillations in Study 301, and 1 monthly instillation in Study 303 (Table 11).

**Table 11. Planned MCNA Exposure (Study 301 and Study 303)**

Study	Treatment Period	Regimen Per Treatment Phase	
		Induction	Maintenance
Study 301	24 months	6 weekly instillations	3 or 6 weekly instillations at Month 3, and 3 weekly instillations at Months 6, 12, 18, and 24 (i.e., every 6 months)
Study 303	12 months	6 weekly instillations	1 monthly instillation for 10 months, starting at Month 3

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

Mean duration of MCNA treatment was 270.8 days and 121.6 days in Study 301 and Study 303, respectively. The mean number of doses of MCNA in Study 301 was 12.3 (98.8% completed), and the mean number of completed doses was 8.3 in Study 303. The recommended retention time of MCNA was 120 minutes in Study 301 and 60 minutes in Study 303. In Study 301, patients were considered to have completed a treatment instillation if bladder retention time was at least 60 minutes. Treatment exposure in Study 301 and Study 303 is summarized in Table 12.

**Table 12. Treatment Exposure (Study 301 and Study 303)**

Measure of Exposure	Study 301 MCNA (N = 129)	Study 303	
		MCNA (N = 39)	Mitomycin C (N = 45)
Duration of treatment (days)			
Number of patients treated	129	37	45
Mean (standard deviation)	270.8 (251.5)	121.6 (99.7)	157.4 (112.3)
Median	156	92	153
Minimum, maximum	1, 783	14, 372	34, 399
Number of doses <sup>a</sup>			
Number of patients	129	37	45
Mean (standard deviation)	12.3 (5.3)	8.3 (3.1)	9.3 (3.3)
Median	12	7	8
Minimum, maximum	1, 24	3, 16	5, 16
Mean retention time (minutes)			
Number of patients	129	37	45
Mean (standard deviation)	130.1 (25.7)	76.6 (27.0)	80.2 (21.8)
Median	125.0	66.3	69.7
Minimum, maximum	53, 201	59, 198	60, 142

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

<sup>a</sup> All doses for Study 301 and completed doses for Study 303.

The duration of cumulative exposure to MCNA extended over 2 years in Study 301, with 127 patients completing the 6 doses of the Induction Phase, 101 patients completing the 3 or 6 doses of Month 3, 48 patients completing Month 6, 36 patients completing Month 12, 28 patients completing Month 18, and 22 patients completing Month 24 (Table 13).

The duration of cumulative exposure to MCNA extended over 1 year in Study 303, with 35 patients completing the Induction Phase, 20 patients completing the monthly dose at Month 3, 10 patients completing Month 6, and 2 patients completing Month 12.

**Table 13. Cumulative Duration of Exposure to MCNA (Study 301 and Study 303)**

Study	N	Number of Patients Who Completed Each Treatment Phase								
		Induction	Maintenance (Month)						18	24
			3 (3) <sup>a</sup>	3 (6) <sup>a</sup>	6	9	12			
301	129	127	71	30	48	NA	36	28	22	
303	37	35	20	NA	10	4	2	NA	NA	

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex; NA = not applicable

<sup>a</sup> Induction therapy in Study 301 could have been repeated (i.e., 6 doses may be given instead of 3).

#### 5.4 Baseline Characteristics

Among the 129 treated patients of Study 301, the median age of study patients was 71 years (range: 41 to 90 years) (Table 14). Most patients were male (95 patients; 73.6%) and all were white. Baseline characteristics were similar in Study 303.

**Table 14. Demographic Characteristics (Study 301 and Study 303, Intent-to-Treat Populations)**

Baseline Characteristic Statistic	Study 301	Study 303	
	MCNA (N = 129)	MCNA (N = 39)	Mitomycin C (N = 45)
Age (years)			
Mean (standard deviation)	68.5 (11.2)	73.0 (8.0)	70.7 (11.2)
Median	71.0	75.0	70.0
Minimum, maximum	41, 90	59, 90	45, 89
Gender, n (%)			
Male	95 (73.6)	34 (87.2)	33 (73.3)
Female	34 (26.4)	5 (12.8)	12 (26.7)
Race			
White	129 (100.0)	39 (100.0)	43 (95.6)
Black or African-American	0	0	1 (2.2)
Asian	0	0	1 (2.2)

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

According to the central pathologist in Study 301, 54 (41.9%) patients had CIS, 30 (23.3%) patients had a combination of CIS and papillary tumor(s) of any grade, 31 (24.0%) patients had papillary tumors only (of these 10, had low grade tumors), 7 (5.4%) patients had no tumor, and 2 (1.6%) patients had no results (Table 15). Within these 129 patients, 5 were determined to have muscle-invasive disease by the central pathologist.

A higher percentage of patients treated with MCNA in Study 303 compared to Study 301 had papillary-only tumors (38.5% versus 24.0%).

**Table 15. Tumor Type (Study 301 and Study 303, Intent-to-Treat Populations)**

Central Pathologist Determination Tumor Type, n (%)	Study 301	Study 303	
	MCNA (N = 129)	MCNA (N = 39)	Mitomycin C (N = 45)
CIS only	54 (41.9)	15 (38.5)	22 (48.9)
CIS and papillary tumors	30 (23.3)	9 (23.1)	6 (13.3)
Papillary only	31 (24.0)	15 (38.5)	17 (37.8)
Muscle-invasive disease	5 (3.9)	0	0
No tumor <sup>a</sup>	7 (5.4)	0	0
Unconfirmed <sup>b</sup>	2 (1.6)	0	0

CIS = carcinoma *in situ*; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

<sup>a</sup> Lack of tumor is due to a discrepancy between local and central pathologists. Three tumors were included as papillary only and 4 were included as CIS only for the primary analysis.

<sup>b</sup> Samples were lost or broken before they could be reviewed by the central pathologist. These tumors were included as CIS only for 1 patient, and as papillary only for 1 patient in the analysis of all treated patients.

In Study 301, all patients had received previous intravesical BCG therapy as required by the protocol; the median time from last BCG treatment to the first dose of MCNA was 204 days (range: 14 to 699 days); 206 days in BCG refractory subgroup and 190.5 days in BCG relapsing subgroup. A total of 45 (34.9%) patients had received previous intravesical chemotherapy; the majority [42 (93.3%)] received mitomycin C.

In Study 303, > 95% of the patients had a prior bladder tumor resection in both treatment groups. All patients were required to have a full induction course of BCG with or without maintenance/re-treatment at 3 months (i.e., qualifying BCG therapy). The median time from last BCG dose of the qualifying therapy to the first MCNA instillation and to first mitomycin C dose was 9.80 months (range: 2.8 to 79.1 months) and 8.90 months (range: 1.6 to 86.8 months), respectively. In addition to the mandatory qualifying BCG therapy, the majority of the patients had received other intravesical immunotherapy prior to the study, mainly additional BCG treatment (71.8% MCNA, 66.7% mitomycin C), while intravesical mitomycin had been used by 5.1% and 8.9% of patients in the MCNA and mitomycin C groups, respectively.

## 5.5 Adverse Events

### 5.5.1 Overview of All Adverse Events

In Study 301, 91.5% of patients experienced at least 1 treatment-emergent adverse event (considered to be drug-related in 65.9% of patients), 63.6% of patients experienced at least 1 local renal/urinary adverse event, and 37.2% experienced at least 1 systemic adverse event (Table 16). The majority of adverse events were local renal and urinary adverse events, with 65 patients reporting events considered to be drug-related to MCNA. Systemic adverse events reported by 34 patients were considered to be drug-related by the investigators.

Serious adverse events were reported for 14.7% of patients and 6.2% of patients had at least 1 adverse event leading to discontinuation of MCNA. A similar profile was observed in Study 303.

**Table 16. Overview of Adverse Events (Study 301 and Study 303, All Treated Patients)**

Number (%) of Patients with at least 1	Study 301	Study 303	
	MCNA (N = 129)	MCNA (N = 37)	Mitomycin C (N = 45)
Adverse event	118 (91.5)	32 (86.5)	35 (77.8)
Drug-related	85 (65.9)	21 (56.7)	21 (46.6)
Local renal/urinary adverse event	82 (63.6)	19 (51.4)	23 (51.1)
Drug-related	65 (50.4)	13 (35.1)	15 (33.4)
Systemic adverse event	48 (37.2)	10 (27.0)	7 (15.6)
Drug-related	34 (26.4)	7 (18.9%)	5 (11.1)
Serious adverse event	19 (14.7)	4 (10.8)	2 (4.4)
Adverse event leading to discontinuation of treatment	8 (6.2)	1 (2.7) <sup>a</sup>	0

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

<sup>a</sup> Event occurred > 30 days after the last instillation of the study medication (not treatment-emergent).

### 5.5.2 Common Adverse Events

In Study 301, most adverse events reported by at least 10% of patients were related to urinary symptoms (hematuria, dysuria, urinary tract infection, pollakiuria [increased urinary frequency], and micturition urgency). Fatigue was the only non-urinary adverse event reported for at least 10% of patients. A similar profile of adverse events was observed in Study 303, but the incidence rates were generally lower. The difference in incidence rates may be due to the longer treatment period in Study 301. Adverse events reported for at least 5% of patients in Study 301 or Study 303 are presented in [Table 17](#).

**Table 17. Adverse Events Reported for at Least 5% of Patients in Study 301 or Study 303 (All Treated Patients)**

Number (%) of Patients with Adverse Event	Study 301	Study 303	
	MCNA (N = 129)	MCNA (N = 37)	Mitomycin C (N = 45)
Hematuria	49 (38.0)	7 (18.9)	3 (6.7)
Dysuria	42 (32.6)	9 (24.3)	12 (26.7)
Fatigue	28 (21.7)	6 (16.2)	3 (6.7)
Urinary tract infection	25 (19.4)	5 (13.5)	5 (11.1)
Pollakiuria	23 (17.8)	6 (16.2)	6 (13.3)
Micturition urgency	17 (13.2)	1 (2.7)	3 (6.7)
Cough	11 (8.5)	1 (2.7)	2 (4.4)
Back pain	12 (9.3)	2 (5.4)	4 (8.9)
Headache	10 (7.8)	1 (2.7)	3 (6.7)
Nausea	10 (7.8)	2 (5.4)	3 (6.7)
Edema peripheral	9 (7.0)	0	2 (4.4)
Nasopharyngitis	9 (7.0)	0	0
Diarrhea	8 (6.2)	3 (8.1)	2 (4.4)
Arthralgia	7 (5.4)	2 (5.4)	1 (2.2)
Asthenia	8 (6.2)	1 (2.7)	2 (4.4)
Nocturia	8 (6.2)	1 (2.7)	0
Nasal congestion	7 (5.4)	1 (2.7)	0
Pyrexia	7 (5.4)	2 (5.4)	0
Anxiety	7 (5.4)	1 (2.7)	1 (2.2)
Insomnia	7(5.4)	0	0
Dry mouth	0	2 (5.4)	0
Chills	6 (4.7)	3 (8.1)	0
Post procedural hematuria	0	2 (5.4)	1 (2.2)
Blood urine present	0	3 (8.1)	1 (2.2)
Pain in extremity	4 (3.1)	2 (5.4)	0
Dizziness	6 (4.7)	3 (8.1)	2 (4.4)
Dyspnea	6 (4.7)	2 (5.4)	1 (2.2)
Hemorrhage urinary tract	0	3 (8.1)	0

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

Most patients had adverse events whose maximum intensity was mild or moderate. In Study 301, 18 (14.0%) patients had severe adverse events. Fatigue was the only adverse event reported as severe for more than 2 patients (3 patients, 2.3%). In Study 303, 1 patient in the MCNA group experienced at least 1 severe adverse event.

### 5.5.3 Local and Systemic Adverse Events in Study 301

In Study 301, regardless of study drug relationship, treatment-emergent local adverse events reported for at least 10% of patients included hematuria, dysuria, urinary tract infection, pollakiuria (increased urinary frequency), and micturition urgency. The most frequently reported drug-related local adverse events were dysuria (32 subjects; 24.8%), hematuria (30 subjects; 23.3%), pollakiuria (18 subjects; 14.0%), micturition urgency (15 subjects; 11.6%) and urinary tract infections (10 patients; 7.8%). Local adverse events reported for at least 5% of patients in Study 301 are presented in Table 18.

**Table 18. Local Adverse Events Reported for at Least 5% of Patients (Study 301, All Treated Patients)**

Number (%) of Patients with Adverse Event	Study 301 MCNA (N = 129)	
	All Events	Drug-Related
Hematuria	49 (38.0)	30 (23.3)
Dysuria	41 (31.8)	32 (24.8)
Urinary tract infection	23 (17.8)	10 (7.8)
Pollakiuria	22 (17.1)	18 (14.0)
Micturition urgency	17 (13.2)	15 (11.6)

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

Most of the drug-related adverse events were of mild and moderate severity (Table 19). Five (3.9%) patients had 7 severe (Grade 3) drug-related adverse events. These events included urinary tract infection, bladder spasm, dysuria, micturition urgency, pollakiuria, and fatigue (2 subjects).

**Table 19. Severity of Drug-Related Adverse Events (Study 301, All Treated Patients)**

<b>Number (%) of Patients with <math>\geq 1</math></b>	<b>MCNA (N = 129)</b>
Drug-related adverse event	85 (65.9)
Mild	45 (34.9)
Hematuria	22 (17.1)
Dysuria	19 (14.7)
Fatigue	17 (13.2)
Micturition urgency	9 (7.0)
Increased urinary frequency	9 (7.0)
Moderate	35 (27.1)
Dysuria	12 (9.3)
Hematuria	8 (6.2)
Increased urinary frequency	8 (6.2)
Severe	5 (3.9)

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

In Study 301, as determined by the investigator, 103 subjects (79.8%) had at least 1 systemic adverse event. Overall, the most common systemic adverse events were fatigue, reported by 27 patients, cough, reported by 11 patients, back pain, headache, and nausea, each reported by 10 patients (Table 20). Fatigue was the only systemic adverse event reported for at least 10% of patients.

**Table 20. Systemic Adverse Events Reported for at Least 5% of Patients in Study 301 (All Treated Patients)**

Number (%) of Patients with Adverse Event	Study 301 MCNA (N = 129)	
	All Events	Drug-Related
Fatigue	27 (20.9)	21 (16.3)
Cough	11 (8.5)	2 (1.6)
Back pain	10 (7.8)	2 (1.6)
Headache	10 (7.8)	3 (2.3)
Nausea	10 (7.8)	4 (3.1)
Edema peripheral	9 (7.0)	1 (0.8)
Nasopharyngitis	9 (7.0)	0
Diarrhea	8 (6.2)	3 (2.3)
Arthralgia	7 (5.4)	2 (1.6)
Asthenia	7 (5.4)	4 (3.1)
Nasal congestion	7 (5.4)	2 (1.6)
Pyrexia	7 (5.4)	4 (3.1)

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

#### 5.5.4 Adverse Events that Resulted in Death

Four patients (3.1%) in Study 301 had adverse events during the study treatment phase that resulted in death and none were considered to be drug-related. One patient each died from cardio-respiratory arrest (began after MCNA treatment ended), multi-organ failure, cerebral hematoma (died within 30 days of the last dose of study drug), and pulmonary fibrosis (died within 60 days of the first dose of study drug). The patient who died from pulmonary fibrosis had a history of the disease. A listing of patients who died is provided in [Section 17](#).

No deaths were reported in Study 303.

#### 5.5.5 Serious Adverse Events Other Than Death

Among the 129 patients who received MCNA in Study 301, 18 patients reported 32 serious adverse events during the period from the first dose of MCNA until 35 days after the last dose. Serious adverse events reported by more than 1 patient in Study 301 included hematuria (3 patients), syncope (2 patients), and chronic obstructive pulmonary disease (2 patients).

There were 2 patients in Study 301 with serious adverse events (urinary tract infection and hematuria) considered drug-related by the investigator. The urinary tract infection was severe (Grade 3) and the hematuria was of moderate severity.

No serious adverse event was reported by > 1 patient in Study 303.

### **5.5.6 Adverse Events Resulting in Study Drug Discontinuation**

In Study 301, 8 (6.2%) patients discontinued treatment due to adverse events. Four of the patients died due to the adverse event (Section 5.5.4). The non-fatal adverse events leading to study drug discontinuation included angina pectoris, asthenia, increased symptoms of Parkinsonism, and vomiting. The events of asthenia and vomiting were considered drug-related by the investigator.

Five patients had adverse events that led to discontinuation from the study. The events included cerebral hematoma, increased symptoms of Parkinsonism, cardio-respiratory arrest, multi-organ failure, and pulmonary fibrosis. Except for Parkinsonism, each adverse event resulted in death.

In Study 303, the only adverse event that was reported as leading to treatment discontinuation (coronary artery disease) occurred > 30 days after the last administration of MCNA. It was considered not related to study drug by the investigator.

### **5.5.7 Adverse Events Resulting in Study Drug Decrease, Interruption, or Delay**

Per protocol, the dose of MCNA was not decreased.

In Study 301, 18 (14.0%) patients had adverse events leading to treatment interruption. The most common adverse events leading to drug interruption were urinary tract infection (4 patients; 3.1%) and hematuria (4 patients; 3.1%).

The primary safety endpoint in Study 301 was the rate of drug-related adverse events leading to 2 consecutive treatment delays of 1 week each or discontinuation of treatment. Three (2.3%) patients met this endpoint and the 95% confidence interval was 0.5% to 6.6%. One patient had 2 consecutive treatment delays due to a urinary tract infection and 2 patients discontinued due to drug-related adverse events (asthenia and vomiting).

In Study 303, adverse events leading to dose delay were experienced by 7 (18.9%) patients in the MCNA group and by 8 (17.8%) patients in the mitomycin C group. Among the patients in the MCNA group, the most common adverse events leading to dose delay were urinary tract infection (2 patients; 5.4%) and hematuria (3 patients; 8.1%). Among the patients in the mitomycin C group, the most common adverse event leading to dose delay was urinary tract infection (2 patients; 4.4%).

### **5.5.8 Adverse Events in Patients Dosed Within 24 Hours of Resection or Biopsy**

MCNA was well tolerated when instilled intravesically within 24 hours of resection or biopsy in a subset of 18 patients. Based on a total of 32 instillations administered to the 18 patients, adverse events were experienced by 28.0% (5/18) of patients following 5 of the 32 instillations (16.0%). In 4 of these 5 instillations, adverse events consisted of hematuria, urinary frequency, dysuria and suprapubic cramps; all events were mild to moderate in severity and not considered drug-related. One patient experienced rigor, nausea and headache with moderate severity after 1 instillation (possibly related to MCNA per the investigator). No adverse events resulted in treatment discontinuation or delays in this group.

## 5.6 Hemoglobin

Hematuria is the presenting symptom in 85% to 90% of patients with bladder cancer and it was a common adverse event reported during the clinical program. Procedures related to the treatment of bladder cancer (such as cystoscopy) can cause hematuria, sometimes making it difficult to ascertain whether hematuria is caused by the procedure or study drug. Changes in blood hemoglobin were reviewed to assess the potential impact of hematuria.

Mean changes from baseline in hemoglobin were small in Study 301, with no consistent trend over time (Table 21). Hemoglobin shifted in 1 patient from Grade 2 at baseline to Grade 3 post-baseline. The patient had experienced Grade 2 hematuria that resolved within 3 days.

In Study 303, hemoglobin shifted from normal at baseline to low at 3 months in 3 patients treated with mitomycin C, to low at 6 months in 2 patients (1 patient treated with MCNA and 1 patient treated with mitomycin C), to low at 9 months in 1 patient treated with mitomycin C, and to low at 12 months in 1 patient treated with MCNA.

**Table 21. Mean Change from Baseline for Hemoglobin (g/dL) (Study 301, Intent-to-Treat Population)**

Time Point	N	Mean (Standard Deviation)	
		Result	Change from Baseline
Baseline	127	13.96 (1.452)	
Week 6	118	13.99 (1.437)	0.01 (0.659)
Month 3	71	14.00 (1.485)	0.00 (1.009)
Month 6	75	13.94 (1.336)	-0.15 (1.069)
Month 12	50	13.96 (1.339)	0.00 (0.868)
Month 18	42	13.97 (1.239)	0.04 (0.970)
Month 24	32	14.03 (1.130)	-0.12 (0.964)
Month 30	20	14.03 (1.605)	0.08 (0.909)
Month 36	18	14.15 (1.562)	-0.16 (0.846)
Month 42	10	13.95 (1.518)	0.15 (0.474)

These results support that treatment with MCNA had no clinically relevant impact on hematuria. In fact, the side effects expected with MCNA are consistent with events associated with treatment procedures (i.e., cystoscopy and resection) and with the use of therapeutic intravesical agents. Urinary symptoms such as pollakiuria (increased urinary frequency), micturition urgency, hematuria, and dysuria are also symptoms associated with bladder cancer and urinary tract infection.

## 5.7 Comparison to Valrubicin

The valrubicin package insert warns that valrubicin should not be administered to patients with a perforated bladder or to those in whom the integrity of the bladder mucosa has been

compromised [Endo 2011]. In contrast, MCNA was well tolerated when instilled intravesically within 24 hours of resection or biopsy in a subset of 18 patients (Section 5.5.8).

Urinary adverse reactions associated with valrubicin usually occurred during or shortly after instillation and resolved within 1 to 7 days after the instillate was removed from the bladder [Endo 2011]. The most common adverse reactions (> 25% of patients) following treatment with valrubicin were urinary frequency, dysuria, urinary urgency, bladder spasm, hematuria, and bladder pain (Table 22). With the exception of hematuria, each event was reported for a smaller percentage of patients in both MCNA studies.

**Table 22. Common Urinary Adverse Events Reported for Valrubicin Compared to MCNA (Study 301 and Study 303, All Treated Patients)**

Adverse Events	MCNA		Valrubicin	
	Study 301 (N = 129)	Study 303 (N = 37)	Pre-Treatment (N = 170)	Post-Treatment (N = 170)
Urinary frequency/pollakiuria	18%	16%	30%	61%
Dysuria	33%	24%	11%	56%
Urinary/micturition urgency	13%	3%	27%	57%
Bladder spasm	3%	3%	3%	31%
Hematuria	38%	19%	11%	29%
Bladder pain	5%	0%	6%	28%

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

Per the package insert, most systemic adverse events associated with the use of valrubicin have been mild in nature and self-limited, resolving within 24 hours after drug administration. Non-urinary adverse events reported by > 2% of valrubicin-treated patients included abdominal pain (5%), nausea (5%), asthenia (4%), headache (4%), malaise (4%), back pain (3%), chest pain (3%), diarrhea (3%), dizziness (3%), and rash (3%).

## 5.8 Risk Discussion and Conclusion

The primary evaluation of safety was based on the 166 patients who received at least 1 administration of MCNA of 8 mg in Studies 301 and 303.

In Study 301, local adverse events reported for at least 10% of patients included hematuria, dysuria, urinary tract infection, pollakiuria (increased urinary frequency), and micturition urgency. Fatigue was the only systemic adverse event reported for at least 10% of patients.

Most patients had adverse events whose maximum intensity was mild or moderate. Eighteen (14.0%) patients had severe adverse events. Fatigue was the only adverse event reported as severe for more than 2 patients (3 patients, 2.3%).

Four patients (3.1%) in Study 301 had adverse events during the study treatment phase that resulted in death, and there were no patient deaths during Study 303. None of the deaths were considered to be drug-related by the investigators.

Bladder-related serious adverse events in Studies 301 and 303 included urinary tract infection, hematuria, bladder spasm, and bladder perforation (reported > 30 days after the final dose of MCNA). There were 2 patients in Study 301 with serious adverse events (urinary tract infection and hematuria) considered drug-related by the investigator. The urinary tract infection was severe (Grade 3) and the hematuria was of moderate severity.

There were no adverse events leading to treatment discontinuation that occurred in more than 1 patient and none of the events were bladder-related.

Hematuria is the presenting symptom in 85% to 90% of patients with bladder cancer and it was a common adverse event reported during the clinical program. However, there was no trend of decreased blood hemoglobin over time in Study 301. In Study 301, hemoglobin shifted in 1 patient from Grade 2 at baseline to Grade 3 post-baseline. The patient had experienced Grade 2 hematuria that resolved within 3 days.

The incidence of adverse events with MCNA compares favorably to that reported in the valrubicin package insert [[Endo 2011](#)], despite the considerably longer follow-up for MCNA (101 patients completing 3 months) versus valrubicin (6-week course of treatment). Also in contrast to valrubicin, MCNA can be administered to patients with compromised integrity of the bladder mucosa (e.g., immediately following resection).

The adverse events observed during treatment with MCNA are familiar to urologists treating NMIBC and can be clinically managed. In conclusion, MCNA was safe and generally well-tolerated during the clinical development program.

## **6 EDUCATION INITIATIVES**

### **6.1 Instructions to Prescribers**

Prescribers will be instructed to:

- Advise the patient to read the approved Patient Information Leaflet.
- Inform the patient that MCNA has been shown to induce a positive response in about 1 in 4 patients. Delaying cystectomy could lead to the development of muscle-invasive and/or metastatic bladder cancer.
- Instruct the patient to report any signs or symptoms of active urinary tract infections.
- Instruct the patient to report signs or symptoms of abdominal discomfort, distension, pain, diarrhea, and vomiting.
- Instruct the patient to report signs of dysuria, hematuria, increased urinary frequency, and urinary urgency.

### **6.2 Proposed Patient Counseling**

#### **6.2.1 Treatment Alternatives**

Patients will be informed that MCNA has been shown to induce a positive response in about 1 in 4 patients. Delaying cystectomy could lead to the development of muscle-invasive and/or metastatic bladder cancer. If cancer is detected, treatment with MCNA may be stopped.

Patients will be informed that there are a number of alternative treatments available that include chemotherapy agents (the use of chemical agents to treat/control a disease), radiation therapy (the use of high-radiation x-rays to treat/control a disease), cystectomy (surgical removal of the bladder, or part of the bladder, and some organs around it), and other investigational therapy if available. Patients also have the right to refuse further treatment.

#### **6.2.2 Procedures Associated with Treatment of Bladder Cancer**

MCNA is put into the bladder through a catheter, and should be kept in the bladder for a minimum of 1 hour before emptying the bladder by going to the bathroom. Tests, such as a cystoscopy or a biopsy, may be performed to assess the extent of bladder cancer.

Cystoscopy is normally performed with a local anesthesia in the urethra, although another type of anesthesia may be given. Before the procedure, an antibiotic may be given to prevent a urinary tract infection that could be caused by the cystoscopy. A sedative may be given before cystoscopy.

Other discomforts or risks associated with cystoscopy and the insertion of the catheter may be experienced. After the cystoscopy, there may be a need to urinate frequently, with some burning during and after urination for a day or two. Blood-colored urine is also common for several days after a cystoscopy, particularly if a biopsy was performed. A mild infection in the urinary tract may also occur. A common but temporary side effect of a cystoscopy is

swelling in the urethra, which may make it difficult to urinate. A urinary catheter may be left in the bladder to help drain the urine until swelling in the urethra has subsided. Another rare complication is a puncture (a cut) of the urethra or bladder by one of the instruments inserted, which requires surgery to repair.

## 7 BENEFIT-RISK ASSESSMENT

Currently, patients with high risk NMIBC are offered only ineffective and unproven treatments or radical cystectomy as the next treatment following BCG failure. Bladder removal is a complex surgery associated with at least 28% to 45% surgical complications and up to 8% mortality, in addition to negatively impacting multiple aspects of quality of life. Patients who refuse or are not medically fit to undergo bladder removal face an increased risk of progression to muscle-invasive disease, likely leading to metastases and death. MCNA offers a new therapeutic option for these patients.

MCNA preserves the patient's bladder without evidence of disease, thus delaying radical cystectomy. In Study 301, 1 in 4 high risk unresponsive bladder cancer patients were disease-free at 1 year, and these patients experienced a long lasting response, preserving the bladder for approximately 3 years.

An important goal in the surveillance and management of high grade NMIBC is to detect progression to muscle-invasive disease at an early time point. For MCNA, we are able to reliably predict progression to muscle-invasion disease using the Month 6 findings. For patients who responded to treatment at 6 months, approximately 85% remained disease-free or have only non-muscle-invasive recurrences by 3 years. Importantly, if a patient did not respond to MCNA at 6 months, the rate of progression was approximately 25% after 3 years, which is similar to historical data, estimated to be 10 to 15% per year, or 30 to 45% after 3 years.

Finally, in comparison to valrubicin, which remains the only FDA-approved non-surgical option for patients with CIS in whom BCG has failed, MCNA was shown to have higher complete response rates in a comparable patient population.

The key challenges in generalizing the efficacy, duration, and safety of MCNA to the larger target population are that Study 301 was a single-arm study, the study included patients with CIS and/or papillary tumors, and the number of patients limits the ability to confidently estimate efficacy in clinically important subpopulations.

With respect to safety and tolerability, the majority of local adverse events were mild to moderate, manageable, and clearly unlike the complications and risks of radical cystectomy. Common local adverse events included hematuria, dysuria, urinary tract infection, pollakiuria (increased urinary frequency), and micturition urgency.

No death was considered by the investigators to be drug-related. Based on safety data from both trials, bladder-related serious adverse events included urinary tract infection, hematuria, bladder spasm, and bladder perforation (reported > 30 days after the final dose of MCNA).

The incidence of adverse events with MCNA compares favorably to that reported for valrubicin, despite the considerably longer follow-up for MCNA. Indeed, the median duration of follow-up from the time of the first dose of treatment to the last evaluation/contact, regardless of response to MCNA treatment, was 34.7 months for the 129 treated patients (range of 0.9 to 60.3 months). Also in contrast to valrubicin, MCNA can be administered to patients with compromised integrity of the bladder mucosa (e.g., immediately following resection).

Regarding the use of a single-arm study, most experts in the field, including those at the 2013 FDA/American Urological Association (AUA) workshop, have concluded that a single-arm design could provide sufficient evidence of benefit, provided that the results were robust. There was also broad consensus at the workshop that studies might include a mix of patients with high grade papillary disease, CIS, and both. This consensus arose from the significant recruitment challenges posed by this patient population. Recognizing the current sample size limitations, Telesta is committed to working with the FDA to establish more firmly the risk-benefit profile of MCNA.

In summary, despite the substantial burden of bladder cancer in the United States, no new intravesical treatments for NMIBC have been approved since valrubicin in 1998. Given that the current therapeutic landscape provides patients with limited and difficult choices and provides clinicians with little flexibility other than moving to radical cystectomy, new treatment options are urgently needed for patients following BCG failure.

MCNA, with its ability to preserve the bladder for 1 out of 4 patients safely and effectively for approximately 3 years, coupled with its relatively benign toxicity profile, provides a significant clinically beneficial treatment option for patients faced with a paucity of choices and a potentially life-altering and life-threatening disease.

## 8 REFERENCE LIST

Author (year)	Reference
ACS (2015)	Cancer Facts & Figures 2015. American Cancer Society. Atlanta, Georgia.
AJCC (2002)	Urinary Bladder in American Joint Committee on Cancer: AJCC Cancer Staging Manual. 6 <sup>th</sup> Edition. New York, NY: Springer 2002, p. 335-40.
AUA (2014)	Guideline for the management of nonmuscle invasive bladder cancer: (stages Ta, T1 and Tis): 2007 Update (Revised February 2014). American Urological Association Guideline 2014.
Avritscher (2006)	Avritscher EB, Cooksley CD, Grossman HB, et al. Clinical model of lifetime cost of treating bladder cancer and associated complications. <i>Urology</i> 2006;68:549-53.
Bohle (2003)	Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guerin versus mitomycin C for superficial bladder cancer: a formal meta-analysis of comparative studies on recurrence and toxicity. <i>J Urol.</i> 2003;169:90-5.
Catalona (1987)	Catalona WJ, Hudson MA, Guillen DP, et al. Risks and benefits of repeated courses of intravesical bacillus Calmette-Guerin therapy for superficial bladder cancer. <i>J Urol.</i> 1987;137:220-4.
Clark (2013)	Clark PE, Agarwal N, Biagioli MC, et al. Bladder cancer. <i>J Natl Compr Canc Netw.</i> 2013;11(4):446-75.
Davis (2002)	Davis JW, Sheth SI, Doviak MJ, et al. Superficial bladder carcinoma treated with bacillus Calmette-Guerin: progression-free and disease specific survival with minimum 10-year follow-up. <i>J Urol.</i> 2002;167:494-500.
Dinney (2013)	Dinney CP, Greenberg RE, Steinberg GD. Intravesical valrubicin in patients with bladder carcinoma in situ and contraindication to or failure after bacillus Calmette-Guérin. <i>Urol Oncol.</i> 2013;31(8):1635-42.
Donat (2009)	Donat SM, Shabsigh A, Savage C, et al. Potential impact of postoperative early complications on the timing of adjuvant chemotherapy in patients undergoing radical cystectomy: a high-volume tertiary cancer center experience. <i>Eur Urol.</i> 2009;55:177-86.
Endo (2011)	Valstar Package Insert. Endo Pharmaceuticals. Chadds Ford, PA. 2011.
Epstein (1998)	Epstein JI, Amin MB, Reuter VR, et al. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. <i>Am J Surg Pathol.</i> 1998;22:1435-48.
Epstein (2003)	Epstein JL. The new World Health Organization/International Society of Urological Pathology (WHO/ISUP) classification for TA, T1 bladder tumors: is it an improvement? <i>Crit Rev Oncol Hematol.</i> 2003;47(2):83-9.
Filion (2001)	Filion MC, Phillips NC. Therapeutic potential of mycobacterial cell wall-DNA complexes. <i>Expert Opin Investig Drugs</i> 2001;10(12):2157-65.
Han (2006)	Han RF, Pan JG: Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. <i>Urology</i> 2006;67:1216.

- Hollenbeck (2007) Hollenbeck BK, Wei, Y, Birkmeyer JD. Volume, process of care, and operative mortality for cystectomy for bladder cancer. *Urology* 2007;69:871-5.
- James (2013) James AC, Gore JL. The costs of non-muscle invasive bladder cancer. *Urol Clin N Am.* 2013;40:261-9.
- Jarow (2014) Jarow JP, Lerner SP, Kluetz PG, et al. Clinical trial design for the development of new therapies for nonmuscle-invasive bladder cancer: report of a Food and Drug Administration and American Urological Association public workshop. *Urology* 2014;83(2):262-4.
- Kamat (2014a) Kamat AM, Witjes JA, Brausi M, et al. Defining and treating the spectrum of intermediate risk nonmuscle invasive bladder cancer. *J Urol.* 2014;192(2):305-15.
- Kamat (2014b) Kamat AM, Porten S. Myths and mysteries surrounding bacillus Calmette-Guérin therapy for bladder cancer. *Eur Urol.* 2014;65(2):267-9.
- Lamm (1989) Lamm DL, Steg A, Boccon-Gibod L, et al. Complications of bacillus Calmette-Guerin immunotherapy: review of 2602 patients and comparison of chemotherapy complications. *Prog Clin Biol Res.* 1989;310:335-55.
- Lamm (2000) Lamm DL, Blumenstein BA, Crissman JD, et al. Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group Study. *J Urol.* 2000;163:1124-9.
- Lerner (2015) Lerner SP, Dinney C, Kamat A, et al. Clarification of bladder cancer disease states following treatment of patients with intravesical BCG. *Bladder Cancer* 2015;1:29-30.
- Morales (1976) Morales A, Eidinger D, Bruce AW. Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. *J Urol.* 1976;116:180-3.
- Morales (2015) Morales A, Herr H, Steinberg G, et al. Efficacy and safety of MCNA in patients with nonmuscle invasive bladder cancer at high risk for recurrence and progression after failed treatment with bacillus Calmette-Guérin. *J Urol.* 2015;193(4):1135-43.
- Oude Elferink (2014) Oude Elferink P, Witjes JA. Blue-light cystoscopy in the evaluation of non-muscle-invasive bladder cancer. *Ther Adv Urol.* 2014;6(1):25-33.
- Raj (2007) Raj GV, Herr H, Serio AM, et al. Treatment paradigm shift may improve survival of patients with high risk superficial bladder cancer. *J Urol.* 2007;177:1283-6.
- Reuter (2006) Reuter VE. The pathology of bladder cancer. *Urology* 2006;67(3 Suppl 1):11-7; discussion 17-8.
- SEER Database Surveillance, Epidemiology, and End Results Program. <http://seer.cancer.gov>. Accessed 31 August 2015.
- Siegel (2015) Siegel R, Miller K, Jemal A. Cancer Statistics, 2015. *CA Cancer J Clin.* 2015;65:5-29.
- Steinberg (2000) Steinberg G, Bahnson R, Brosman S, et al. Efficacy and safety of valrubicin for the treatment of Bacillus Calmette-Guerin refractory carcinoma in situ of the bladder. The Valrubicin Study Group. *J Urol.* 2000;163(3):761-7.
- Sylvester (2002) Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical



## 9 KEY REGULATORY HISTORY

The IND for MCNA was submitted on 02 December 2005 by Bioniche Life Sciences Inc. (renamed as Telesta Therapeutics Inc. in 2014). Three clinical trial protocols were submitted under this application and major regulatory filings and events related to the current proposed indication in second line therapy are described below:

- The protocol for Study 301 (refractory indication) was submitted on 02 December 2005. Fast Track designation was granted on 28 April 2006. The clinical study report was submitted on 13 July 2012.
- Sponsorship of the IND was transferred to Endo Pharmaceuticals Inc. on 05 August 2009.
- The protocol for Study 303 was submitted on 04 October 2010. Due to enrollment difficulties related to the study design of this comparative trial against mitomycin C, Fast Track discussions were held with the FDA. These Fast Track discussions led the sponsor to consider alternatives to the current design of Study 303, narrowing the design options to a single-arm trial design. A meeting to discuss the study design was held with the FDA on 12 October 2012, and no agreement could be reached on a new study design. Study 303 was stopped on 02 November 2012 due to logistical problems with patient enrollment. The clinical study report was submitted on 13 March 2014.
- Sponsorship of the IND was transferred to Telesta on 01 April 2013.
- A meeting with the FDA was requested on 13 December 2013 to review and discuss the data generated up to that point on MCNA and to obtain agreement on the data's adequacy to support the filing of a Biologics License Application (BLA) under the Accelerated Approval Program. The FDA responded on 19 February 2014 that they did not consider the data package to be adequate for consideration under the Accelerated Approval program. The FDA highlighted that the pre-specified endpoint of disease-free survival of 40% had not been met in Study 301, and that the lower bounds of the confidence intervals for disease-free survival were modest.
- Telesta responded that the results, while not meeting the pre-specified criterion of 40%, were still clinically meaningful in this patient population which has limited treatment options. For those patients who responded to treatment, the disease-free duration was durable, and for patients who did not respond, the risk of progression was not higher than expected using historical averages. Overall, Telesta's position was that the results were clinically meaningful and sufficient to support a full marketing application for the treatment of NMIBC at high risk of recurrence and progression (CIS and/or high grade papillary tumors) who had failed prior BCG.
- On 16 July 2014, the FDA agreed that a submission was appropriate with final assessment of approvability being a review issue.

- On 24 November 2014, a pre-BLA meeting was held with the Office of Cellular, Tissue and Gene Therapy to discuss the planned BLA submission for MCNA and to obtain concurrence with the Agency on the BLA components.
- On 12 February 2015, a Type C Facilities meeting was held with Division of Manufacturing and Drug Quality to discuss facility-related topics with the Agency in advance of filing the BLA.
- The BLA for MCNA was submitted on 29 June 2015 and was granted Priority Review classification on 27 August 2015.

**10 EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS**

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

## 11 ENTRY CRITERIA FOR STUDIES 301 AND 303

Study 301	Study 303
<b>Inclusion Criteria</b>	
Male and female subjects, 18 years of age and over	Males and females who are 18 years of age or older at time of consent signing
<p>Subjects who were refractory to BCG</p> <p>Refractory was defined as evidence of persistent high grade bladder cancer after at least 6 months had elapsed following the start of a full induction course of BCG1 with or without maintenance or re-treatment at 3 months.</p> <p>Refractory was also defined as evidence of relapsing high grade bladder cancer within 2 years from the start of a full induction course of BCG (subject received 75% of the total expected treatment dose of BCG within a period of 2 months) and after achieving a disease-free status 6 months post-induction. The relapsing high grade tumor must have been evident within 6 months after receiving a dose of BCG therapy.</p>	<p>Have either BCG relapsing or refractory NMIBC:</p> <p>Refractory disease was defined as evidence of persistent high grade bladder cancer –(TaHG, T1, and/or CIS) at least 6 months from the start of a full induction course of BCG (at least 5 out of 6 total expected instillations of BCG within a period of 2 months, regardless of dose strength) with or without maintenance/re-treatment at 3 months.</p> <p>Relapsing disease was defined as reappearance of disease after achieving a tumor-free –status by 6 months following a full induction course of BCG1 with or without maintenance/re-treatment at 3 months. Subjects with relapsing disease must have recurred within 18 months following the last dose of BCG.</p>
<p>Subjects with one of the following histologically confirmed diagnoses according to the local pathologist:</p> <p>High grade Ta and/or T1 papillary lesions</p> <p>CIS, with or without Ta or T1 papillary tumor(s) of any grade</p> <p>Resection or biopsy specimen used to diagnose T1 stage must include a portion of the underlying muscle to confirm stage.</p> <p>If applicable, have had all visible papillary lesions resected by resection within 56 days prior to beginning of study treatment</p>	<p>Have histologically confirmed NMIBC (according to 2004 WHO classification) within 8 weeks prior to randomization:</p> <p>High grade Ta papillary lesion(s)</p> <p>High or low grade T1 papillary lesion(s) (biopsy sample must include evidence of muscularis propria)</p> <p>CIS, with or without Ta or T1 papillary tumor(s) of any grade</p>
<p>Histologically confirmed diagnosis of high grade disease must be within 56 days prior to beginning of treatment</p>	<p>Have had all visible papillary and resectable CIS lesion(s) removed by resection within 8 weeks prior to randomization</p>
<p>Available for the whole duration of the study including follow-up (60 months)</p>	<p>Available for the duration of the study including follow-up (approximately 36 months)</p>
<p>Life expectancy of &gt;5 years</p>	
<p>Subjects with an Eastern Cooperative Oncology Group (ECOG) performance status grade of 2 or less</p>	<p>Have an Eastern Cooperative Oncology Group (ECOG) performance status grade of 2 or less</p>

Study 301	Study 303
Absence of urothelial carcinoma involving the upper urinary tract or prostatic urethra (confirmed by upper tract radiological imaging and/or biopsy) within 12 months from beginning of study treatment	Have no evidence of urothelial carcinoma involving the upper urinary tract or the urethra (confirmed by extravesical workup, which may include radiological imaging and/or biopsy) within 6 months prior to randomization:
	If previous workup occurred more than 6 months prior to randomization, extravesical workup must be repeated prior to randomization in order to determine eligibility
Able to understand and give written informed consent	Is able to understand and give written informed consent
In the Investigator’s judgment, the subject was able to participate in the study	
<b>Exclusion Criteria</b>	
Current or previous history of muscle invasive bladder tumors ( $\geq T2$ )	Current or previous history of muscle invasive bladder tumors
Current or previous history of lymph node or distant metastases from bladder cancer	Current or previous history of positive lymph nodes and/or metastatic bladder cancer
	Current evidence of pure squamous cell carcinoma, pure adenocarcinoma or pure undifferentiated carcinoma of the bladder
Current systemic cancer therapy (cytotoxic/cytostatic or immunotherapy)	Currently receiving systemic anti-cancer therapy (cytotoxic/cytostatic or immunotherapy)
	Currently receiving treatment with a prohibited therapy (as per protocol’s section on Prohibited Medications)
	Systemic immunotherapy within 6 months of randomization
	Prior treatment with an intravesical chemotherapeutic agent within 3 months of randomization, with the exception of a single perioperative dose of chemotherapy immediately post-resection (not considered treatment)
	Current or prior history of systemic lupus erythematosus
Current or prior pelvic external beam radiotherapy	
Pelvic brachytherapy within 2 years of study entry	
Prior treatment with MCC (EN3348)	Prior treatment with MCNA suspension (formerly known as MCC or EN3348 •suspension) or any other mycobacterial cell wall composition or formulation

Study 301	Study 303
<p>Subjects with existing urinary tract infection or relapsing severe bacterial cystitis</p>	<p>Refractory to mitomycin C (failure to achieve tumor-free status following minimum of a 6-week induction course of mitomycin C) at any time in the subject's disease history</p> <p>Contraindication to mitomycin C</p>
<p>Clinically significant and unexplained elevations of liver or renal function tests</p>	<p>Untreated urinary tract or bladder infection</p>
<p>White blood cell (WBC) count below <math>3 \times 10^9/L</math> (<math>3,000/mm^3</math>) or platelet count below <math>100 \times 10^9/L</math> (<math>100,000/mm^3</math>)</p>	<p>ANC (absolute neutrophil count) <math>&lt;1000/\mu L</math> and hemoglobin <math>&lt;10</math> g/dL</p>
<p>Severe cardiovascular disease such as myocardial infarction within the past 3 months, unstable angina pectoris, congestive heart failure (New York Heart Association [NYHA] Class III or IV), or uncontrolled cardiac arrhythmia</p>	<p>Known cardiovascular disease such as myocardial infarction within the past 3 months, unstable angina pectoris, congestive heart failure (New York Heart Association [NYHA] Class III or IV) or uncontrolled cardiac arrhythmia</p>
<p>Women who are pregnant or lactating. Women of childbearing potential must use an effective contraceptive method such as oral contraceptive pills, diaphragm, or condoms. A woman of childbearing potential was defined as one who was biologically capable of becoming pregnant (exclusion criterion)</p>	<p>Subjects (male and female) of child-bearing potential (including female subjects who are post-menopausal for less than 1 year) must be willing to practice effective contraception (as defined by the investigator) while on treatment and be willing and able to continue contraception for 30 days after their last dose of study treatment (inclusion criterion)</p> <p>Female subjects who are pregnant or lactating</p>
<p>Congenital or acquired immune deficiency</p>	<p>Congenital or acquired immune deficiency</p>
<p>With history of malignancy of any organ system, treated or untreated, within the past 5 years (with the exception of adequately treated basal cell or squamous cell carcinoma of the skin, stage T1 prostate cancer, carcinoma in situ of the cervix, colon polyps)</p>	<p>Have current or history of documented or suspected malignancy of any organ system (diagnosed, treated or untreated) within the past 5 years (with the exception of localized transitional cell carcinoma of the ureter treated with ureterectomy or nephroureterectomy, adequately treated basal cell or squamous cell carcinoma of the skin or asymptomatic non-metastatic prostate cancer either previously successfully treated or currently under active surveillance or receiving hormone therapy only)</p>
<p>Previous investigational treatment within 3 months from beginning of study treatment</p>	<p>Treatment with an investigational agent within 30 days or 5 half-lives from randomization, whichever is longer</p>
<p>Subjects who could not hold the instillation for 1 hour</p>	<p>Bladder contracture or history of an inability to retain the instillate for a minimum of 1 hour, even with premedication</p>
<p>Subjects who could not tolerate intravesical administration or intravesical surgical manipulation (cystoscopy or biopsy)</p>	<p>Inability to tolerate intravesical administration or intravesical surgical manipulation (cystoscopy or biopsy)</p>

<b>Study 301</b>	<b>Study 303</b>
Clinically significant active infections Any medical or psychiatric condition which, in the opinion of the Investigator, would have precluded the participant from adhering to the protocol or completing the trial per protocol	Clinically significant active infections Any medical or psychiatric condition which, in the opinion of the investigator, would preclude the participant from adhering to the protocol or completing the trial per protocol

## **12 SCHEDULE OF PROCEDURES**

### **12.1 Study 301 Schedule of Procedures**

Evaluations	Baseline (3-56 days from Week 1 visit)	Induction Phase Week 1 to Week 6 - every 7 (-1/+3) days					
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Informed consent	X						
Pregnancy Test (if applicable)	X						
Medical history	X						
Vital signs (BP, pulse, T°)	X	X	X	X	X	X	X
Hematology	X						X
Clinical chemistry	X						X
Urinalysis	X						X
Urine dipstick/culture <sup>1</sup>	X						
Urine cytology	X						
Biopsy	X						
Cystoscopy	X						
Concomitant medications	X	X	X	X	X	X	X
Physical exam, height, body weight	X						
MCC (EN3348) administration <sup>2</sup>		X <sup>3</sup>	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X

<sup>1</sup> In subjects with positive culture, study treatment was postponed until a negative culture was obtained.

<sup>2</sup> Every effort was made for the MCC (EN3348) suspension to be retained in the bladder for at least 2 hours.

<sup>3</sup> The first instillation must have occurred at a minimum of 7 days and a maximum of 56 days following TURBT or biopsy.

Evaluations	Maintenance Phase (Every 3 months ± 1 week)								Per-Protocol or Early Discontinuation <sup>9</sup>	Follow-Up Phase (Every 6 months ± 2 weeks)					Month 60/ End of Study <sup>11</sup>
	Month 3 <sup>7</sup>	Month 6 <sup>8</sup>	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24		Month 30	Month 36	Month 42	Month 48	Month 54	
Vital signs (BP, pulse, T°)	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Hematology <sup>1</sup>	X	X		X		X		X		X	X	X	X	X	X
Physical Examination															X
Pregnancy Test (if applicable)															X
Clinical chemistry <sup>1</sup>	X	X		X		X		X		X	X	X	X	X	X
Urinalysis <sup>1</sup>	X	X		X		X		X		X	X	X	X	X	X
Urine dipstick/culture <sup>2</sup>															
Urine cytology <sup>3</sup>	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Biopsy <sup>4</sup>	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Cystoscopy <sup>5</sup>	X	X	X	X	X	X	X	X		X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X						
MCC (EN3348) administration <sup>6</sup>	X	X		X		X		X							
Adverse events	X	X	X	X	X	X	X	X	X						
Additional subject information <sup>10</sup>										X	X	X	X	X	X

<sup>1</sup> During the maintenance phase, blood and urine samples were collected only once at months 3, 6, 12, 18, and 24, preferably before the last of the 3 instillations.

<sup>2</sup> In subjects with positive culture, study treatment was postponed until a negative culture was obtained.

<sup>3</sup> Urine for cytology must have been collected before cystoscopy. During maintenance phase, urine was to be collected only once at months 3, 6, 12, 18, and 24.

<sup>4</sup> Biopsies were mandatory at month 6 for all subjects. During study, TURBTs/biopsies were to be done in case of evident or suspicious lesions by cystoscopy or positive urine cytology.

<sup>5</sup> During the maintenance phase, cystoscopies were to be performed only once at months 3, 6, 12, 18, and 24, preferably before the first of the 3 instillations.

<sup>6</sup> During the maintenance phase, 3 weekly instillations were to be given at months 3, 6, 12, 18, and 24. The MCC (EN3348) suspension should have been retained in the bladder for at least two hours.

<sup>7</sup> Subjects who were not disease-free at month 3, but had not progressed, were to receive either a second 6-week induction or a 3-week maintenance course at this visit. Subjects with high grade T1 tumor(s) at study entry may or may not have received a second Induction course at this visit if they had persistent high grade T1 tumor(s). If any of these subjects were disease-free at month 6, they were to enter the maintenance phase and were to then follow the same study schedule as the other subjects.

<sup>8</sup> The month 6 visit time-window might have differed from the other visits within the maintenance phase for subjects that received a second induction course at month 3. In this case, the month 6 visit should have occurred no later than 6 weeks from the last instillation of the second Induction course.

<sup>9</sup> A follow-up telephone call was to be made at 30 (+5) days from the subject's last treatment on the study to assess the occurrence of any AEs/serious adverse events (SAEs) and the intake of AE-related concomitant medications. If indicated, a clinic visit may have taken place.

<sup>10</sup> Information such as bladder cancer treatments, cystectomies, second primary cancers and survival status continued to be collected during the follow-up phase.

<sup>11</sup> Follow-up phase was variable based on when the subject was enrolled in the study. Follow-up phase was up to 60 months. All subjects were to have an End of Study visit conducted either in the clinic or by telephone contact.

## **12.2 Study 303 Schedule of Procedures**

**Screening/Induction**

Procedures/Assessments	Screening Phase (-8 weeks <sup>7</sup> )	Induction Phase					
		Week 1 to Week 6 – every 7 days (-1 or +3 days)					
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Extravesical work up	X <sup>1</sup>						
Urine cytology <sup>2</sup>	Local lab						
Cystoscopy <sup>2</sup>	X						
TURBT/biopsy <sup>2</sup>	X <sup>2</sup>						
Obtain written informed consent	X						
Review of eligibility criteria	X						
Pathology <sup>3</sup>	Central path. <sup>4</sup>						
Urine pregnancy test (if applicable)	Dipstick						
Demographics	X						
Medical history	X						
ECOG performance status	X						
Bladder cancer history and treatment	X						
Vital signs	X	X	X	X	X	X	X
Physical examination	X						
Clinical lab tests <sup>3</sup>	X						
Blood sample for anti-MCNA antibody testing		X <sup>8</sup>					
Confirm eligibility	X <sup>9</sup>						
Randomization		X					
Record previous/concomitant medications	X	X	X	X	X	X	X
Serious adverse events/adverse events	X <sup>5</sup>	X	X	X	X	X	X

Procedures/Assessments	Screening Phase (-8 weeks <sup>7</sup> )	Induction Phase					
		Week 1 to Week 6 – every 7 days (-1 or +3 days)					
		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
MCNA or mitomycin C instillation <sup>6</sup>		X	X	X	X	X	X

- <sup>1</sup> Extravesical work up completed within 6 months prior to randomization and no evidence of disease was reported.
- <sup>2</sup> Urine cytology (voided only, no bladder washing), cystoscopy and transurethral resection of bladder tumor (TURBT)/biopsy performed per standard of care prior to consent; and sample read by local pathology to determine if there was evidence of disease.
- <sup>3</sup> All protocol-specified clinical laboratory tests and pathology specimens were centrally reviewed and reports issued.
- <sup>4</sup> After subject has signed informed consent, slides read by local pathology must have been sent to central pathology to determine eligibility for the study.
- <sup>5</sup> Adverse events (AEs) were captured from time of informed consent signature.
- <sup>6</sup> The first instillation must have occurred within 3 days of randomization; any instillation may have been delayed up to 2 consecutive weeks (refer to section 10 of protocol, Treatment of Subjects, for details).
- <sup>7</sup> Screening phase may have been extended to 12 weeks for subjects needing a re-TURBT to obtain tissue from the muscularis propria (required for T1 papillary disease).
- <sup>8</sup> Blood sample drawn after randomization and before first instillation.
- <sup>9</sup> Must have been done prior to randomization.

Maintenance/Follow-Up

Evaluations	Maintenance Phase (+2 weeks)										Follow-Up Phase	End of Study
	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12/ End of Treatment	Every 3 months (mo 13-24); every 6 months (mo 25-36)	
Vital signs	X	X	X	X	X	X	X	x	x	X	X <sup>7</sup>	X
Physical examination										X		X
Urine pregnancy test (if applicable)				Dipstick						Dipstick		Dipstick
Clinical lab tests (central) <sup>1</sup>	X			X			X			X		
Blood sample for anti-MCNA antibody testing										X <sup>8</sup>		
Urine cytology (local) <sup>2</sup>	X			X			X			X	X	X
Cystoscopy	X			X			X			X	X	X
TURBT/biopsy <sup>3</sup>	X			X			X			X	X	X
Pathology <sup>1</sup>	X			X			X			X	X	X
Record serious adverse events/adverse events	X	X	X	X	X	X	X	X	X	X	X <sup>4</sup>	
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X <sup>5</sup>	
MCNA or mitomycin C instillation <sup>9</sup>	X	X	X	X	X	X	X	X	X	X		
Follow-Up data collection <sup>6</sup>											X	X

- <sup>1</sup> All clinical laboratory tests and pathology specimens were analyzed/reviewed centrally.
- <sup>2</sup> Aside from specific time points in the Schedule of Assessments, cytology could be performed at any time if symptoms were present and was the best practice in the opinion of the investigator. All urine cytology was read by local pathology laboratory.
- <sup>3</sup> Month 6 biopsy was mandatory, regardless of cytology and cystoscopy results. At other time points, transurethral resection of bladder tumor (TURBT)/biopsy was performed if indicated, based on either positive cytology or cystoscopy.
- <sup>4</sup> Adverse events (AEs)/serious adverse events (SAEs) were to be captured for 30 days following last dose. After the 30-day limit, SAEs were only to be captured if the investigator considered the event to be related to treatment.
- <sup>5</sup> Were captured medications used to treat SAEs and new anti-cancer therapies.
- <sup>6</sup> Included data for disease recurrence, progression to muscle invasive disease, secondary malignancy, cystectomy, additional anti-cancer therapies, other surgeries, and overall survival.
- <sup>7</sup> Only for 30 days after the last dose of study drug.
- <sup>8</sup> Blood sample drawn after the last instillation.
- <sup>9</sup> Investigators must have waited a minimum of 5 days before dosing subjects after TURBT/biopsy (refer to section 8.3 of protocol, Study Drug and Administration).

### 13 EFFICACY RESULTS FOR STUDY 303

The planned primary efficacy endpoint of Study 303 was event-free survival, defined as the interval from randomization to the occurrence of tumor recurrence, tumor progression to muscle-invasive bladder cancer, or death due to any reason, whichever occurred first. The planned secondary efficacy endpoints were the event-free survival rate at 1 and 2 years, recurrence rate at 1 and 2 years, the progression rate at 1 and 2 years, the time to cystectomy, and overall survival. However, these endpoints were not evaluated due to enrollment difficulties, which resulted in early study termination. Descriptive statistics of complete response, standard cystoscopy, and urine cytology are presented.

The complete response rate was 17.4% at Month 6 for patients in the MCNA group with CIS with or without papillary tumors (Table 23). For patients with CIS disease only at baseline, the complete response rate was 21.4% at Month 6.

**Table 23. Complete Response to MCNA (Study 303, Intent-to-Treat Population With CIS With or Without Papillary Tumors)**

		<b>MCNA (N = 39)</b>	
<b>Visit Finding</b>	<b>N</b>	<b>% (95% Confidence Interval)</b>	
<b>Month 3</b>			
CIS with or without papillary	23	47.8 (26.8, 69.4)	
CIS + papillary	9	33.3 (7.5, 70.1)	
CIS only	14	57.1 (28.9, 82.3)	
<b>Month 6</b>			
CIS with or without papillary	23	17.4 (5.0, 38.8)	
CIS + papillary	9	11.1 (0.3, 48.2)	
CIS only	14	21.4 (4.7, 50.8)	

CIS = carcinoma *in situ*; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

The proportion of patients in the MCNA treatment group with cystoscopically detectable CIS and/or papillary tumor decreased from 94.9% at screening to 39.3% at Month 3, and to 25.0% at Month 6 (Table 24). Similarly, the proportion of patients in the mitomycin C group with a detectable CIS and/or papillary tumor was 95.6% at screening, 18.8% at Month 3, and 22.7% at Month 6.

**Table 24. Cystoscopy Results (Study 303, Intent-to-Treat Population)**

<b>Visit Finding</b>	<b>MCNA (N = 39)</b>	<b>Mitomycin C (N = 45)</b>
Screening, n (%)		
CIS and/or papillary tumors visualized	37 (94.9)	43 (95.6)
Resection of papillary tumors	25 (67.6)	21 (61.8)
Month 3, n (%)		
CIS and/or papillary tumors visualized	11 (39.3)	6 (18.8)
Resection of papillary tumors	3 (15.0)	2 (11.1)
Month 6, n (%)		
CIS and/or papillary tumors visualized	4 (25.0)	5 (22.7)
Resection of papillary tumors	2 (14.3)	3 (18.8)

CIS = carcinoma *in situ*; MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

At screening, the results of urine cytology were negative for 48.7% of the patients in the MCNA treatment group and 34.1% of patients in the mitomycin C group, while the proportion of patients with suspicious results was 5.1% in the MCNA group and 22.7% in the mitomycin C group (Table 25). At Month 3, the results for negative and suspicious urine cytology were comparable between the treatment groups, but were higher for malignant cytology in the mitomycin C group (12.5% versus 3.6% for MCNA) and higher for atypical cytology in the MCNA group (32.1% versus 12.5% for mitomycin C). At Month 6, no remarkable differences in urine cytology were observed with 66.7% and 72.7% of patients in the MCNA and mitomycin C group, respectively, having negative cytology results. Overall, from screening to Month 6, the percentage of patients with negative cytology results increased in both treatment groups.

**Table 25. Cytology Results (Study 303, Intent-to-Treat Population)**

<b>Visit Finding</b>	<b>MCNA (N = 39)</b>	<b>Mitomycin C (N = 45)</b>
Screening, n (%)	n = 39	n = 44
Malignant	5 (12.8)	5 (11.4)
Suspicious	2 (5.1)	10 (22.7)
Atypical	13 (33.3)	14 (31.8)
Negative	19 (48.7)	15 (34.1)
Unsatisfactory specimen	0	0
Month 3, n (%)	n = 28	n = 32
Malignant	1 (3.6)	4 (12.5)
Suspicious	2 (7.1)	3 (9.4)
Atypical	9 (32.1)	4 (12.5)
Negative	16 (57.1)	21 (65.6)
Unsatisfactory specimen	0	0
Month 6, n (%)	n = 15	n = 22
Malignant	1 (6.7)	0
Suspicious	0	2 (9.1)
Atypical	3 (20.0)	3 (13.6)
Negative	10 (66.7)	16 (72.7)
Unsatisfactory specimen	1 (6.7)	1 (4.5)

MCNA = Mycobacterium phlei Cell Wall-Nucleic Acid Complex

**14 LOCAL PATHOLOGIST ASSESSMENTS FOR STUDY 301**

**Table 26. Kaplan-Meier Estimates of Disease-Free Survival by Baseline Tumor Stage in Study 301 as Assessed by the Local Pathologist**

	N	Number of Months from Baseline				
		3	6	12	18	24
ITT Population, % (95% CI)						
Overall	129	67.1 (58.2, 74.5)	39.5 (30.8, 48.0)	26.6 (19.0, 34.7)	20.6 (13.8, 28.3)	16.8 (10.6, 24.2)
CIS/CIS+Pap	79	67.1 (55.6, 76.3)	39.6 (28.7, 50.3)	22.4 (13.9, 32.3)	14.5 (7.7, 23.3)	11.3 (5.3, 19.8)
CIS Only	54	74.1 (60.2, 83.7)	54.7 (40.4, 66.9)	29.3 (17.7, 41.9)	21.5 (11.5, 33.5)	16.7 (7.9, 28.4)
CIS+Pap	25	52.0 (31.2, 69.2)	16.0 (5.0, 32.5)	8.0 (1.4, 22.5)	NE	NE
Pap Only	50	66.7 (51.5, 78.1)	39.9 (25.7, 53.7)	34.9 (21.3, 48.8)	32.4 (19.2, 46.3)	27.4 (15.2, 41.2)

CI = confidence interval; CIS = carcinoma *in situ*; ITT = intent-to-treat; NE = not estimable; Pap = papillary

**Table 27. Kaplan-Meier Estimates of Disease-Free Survival by BCG Failure Type in Study 301 as Assessed by the Local Pathologist**

	N	Number of Months from Baseline				
		3	6	12	18	24
ITT Population, % (95% CI)						
Relapsing	22	72.7 (49.1, 86.7)	49.0 (26.9, 67.8)	39.2 (19.1, 58.8)	34.3 (15.5, 54.1)	34.3 (15.5, 54.1)
Refractory	107	65.9 (56.0, 74.1)	37.4 (28.0, 46.8)	23.9 (16.0, 32.7)	17.7 (10.9, 25.8)	12.9 (7.0, 20.5)
ITT Population – Papillary only, % (95% CI)						
Relapsing	7	71.4 (25.8, 92.0)	71.4 (25.8, 92.0)	53.6 (13.2, 82.5)	53.6 (13.2, 82.5)	53.6 (13.2, 82.5)
Refractory	43	65.9 (49.3, 78.2)	34.5 (20.1, 49.3)	31.6 (17.7, 46.5)	28.7 (15.4, 43.5)	23.0 (11.1, 37.4)
ITT Population – CIS with or without papillary, % (95% CI)						
Relapsing	15	73.3 (43.6, 89.1)	40.0 (16.5, 62.8)	33.3 (12.2, 56.4)	NE	NE
Refractory	64	65.6 (52.6, 75.8)	39.5 (27.4, 51.3)	19.8 (10.9, 30.5)	11.5 (5.1, 20.9)	6.9 (2.1, 15.9)
ITT Population – CIS only, % (95% CI)						
Relapsing	9	77.8 (36.5, 93.9)	66.7 (28.2, 87.8)	55.6 (20.4, 80.5)	NE	NE
Refractory	45	73.3 (57.8, 83.9)	47.5 (32.1, 61.3)	23.7 (12.3, 37.2)	16.6 (7.3, 29.2)	10.0 (2.9, 22.2)
ITT Population – CIS and papillary, % (95% CI)						
Relapsing	6	66.7 (19.5, 90.4)	NE	NE	NE	NE
Refractory	19	47.4 (24.4, 67.3)	21.1 (6.6, 41.0)	10.5 (1.8, 28.4)	NE	NE

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma *in situ*; ITT = intent-to-treat; NE = not estimable

**Table 28. Kaplan-Meier Estimates of Disease-Free Survival by BCG Instillation Group in Study 301 as Assessed by the Local Pathologist**

	N	Number of Months from Baseline				
		3	6	12	18	24
ITT Population, % (95% CI)						
≤ 6 instillations	32	71.7 (52.7, 84.2)	32.6 (17.2, 49.0)	22.8 (10.1, 38.6)	16.3 (6.0, 31.2)	16.3 (6.0, 31.2)
7 - 12 instillations	52	70.4 (55.8, 81.0)	50.0 (35.4, 62.9)	33.3 (20.6, 46.5)	22.9 (12.3, 35.4)	13.7 (5.7, 25.2)
≥ 13 instillations	45	60.0 (44.3, 72.6)	31.9 (18.4, 46.3)	21.3 (10.2, 35.1)	21.3 (10.2, 35.1)	21.3 (10.2, 35.1)
ITT Population – Papillary only, % (95% CI)						
≤ 6 instillations	13	91.7 (53.9, 98.8)	41.7 (15.2, 66.5)	41.7 (15.2, 66.5)	NE	NE
7 - 12 instillations	23	63.6 (40.3, 79.9)	45.0 (23.9, 64.1)	35.0 (16.1, 54.7)	35.0 (16.1, 54.7)	25.0 (9.3, 44.6)
≥ 13 instillations	14	50.0 (22.9, 72.2)	33.3 (10.9, 58.0)	33.3 (10.9, 58.0)	33.3 (10.9, 58.0)	33.3 (10.9, 58.0)
ITT Population – CIS with or without papillary, % (95% CI)						
≤ 6 instillations	19	57.9 (33.2, 76.3)	26.3 (9.6, 46.8)	10.5 (1.8, 28.4)	5.3 (0.4, 21.4)	5.3 (0.4, 21.4)
7 - 12 instillations	29	75.9 (55.9, 87.7)	54.2 (34.4, 70.3)	32.5 (16.4, 49.8)	14.4 (4.6, 29.8)	NE
≥ 13 instillations	31	64.5 (45.2, 78.5)	34.2 (18.1, 50.9)	20.5 (8.4, 36.3)	20.5 (8.4, 36.3)	20.5 (8.4, 36.3)
ITT Population – CIS only, % (95% CI)						
≤ 6 instillations	12	75.0 (40.8, 91.2)	33.3 (10.3, 58.8)	8.3 (0.5, 31.1)	8.3 (0.5, 31.1)	8.3 (0.5, 31.1)
7 - 12 instillations	24	75.0 (52.6, 87.9)	61.8 (39.3, 78.0)	35.3 (17.0, 54.3)	17.6 (5.5, 35.3)	NE
≥ 13 instillations	18	72.2 (45.6, 87.4)	48.1 (23.9, 68.9)	36.1 (15.0, 57.9)	36.1 (15.0, 57.9)	36.1 (15.0, 57.9)
ITT Population – CIS and papillary, % (95% CI)						
≤ 6 instillations	7	28.6 (4.1, 61.2)	14.3 (0.7, 46.5)	14.3 (0.7, 46.5)	NE	NE
7 - 12 instillations	5	80.0 (20.4, 96.9)	20.0 (0.8, 58.2)	20.0 (0.8, 58.2)	NE	NE
≥ 13 instillations	13	53.8 (24.8, 76.0)	15.4 (2.5, 38.8)	NE	NE	NE

BCG = bacillus Calmette-Guérin; CI = confidence intervals; CIS = carcinoma *in situ*; ITT = intent-to-treat; NE = not estimable

**Table 29. Complete Response Rate Over Time in Patients with CIS in Study 301 as Assessed by the Local Pathologist**

	N	Number (%) Subjects with Complete Response		
		6 Months	12 Months	24 Months
ITT Population, % (95% CI)	129	38.0 (29.6, 46.9)	24.0 (16.9, 32.3)	13.2 (7.9, 20.3)
CIS with or without papillary	79	40.5 (29.6, 52.1)	21.5 (13.1, 32.2)	8.9 (3.6, 17.4)
CIS only	54	51.9 (37.8, 65.7)	27.8 (16.5, 41.6)	13.0 (5.4, 24.9)
CIS with papillary	25	16.0 (4.5, 36.1)	8.0 (1.0, 26.0)	0

CI = confidence interval; CIS = carcinoma *in situ*; ITT = intent-to-treat

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**Table 30. Kaplan-Meier Estimates of Disease-Free Survival by Baseline Tumor Stage in Study 301 as Assessed by the Central Pathologist**

	N	Number of Months from Baseline				
		3	6	12	18	24
ITT Population, % (95% CI)						
Overall	129	62.4 (53.3, 70.1)	38.0 (29.5, 46.6)	23.7 (16.5, 31.6)	18.6 (12.2, 26.0)	16.9 (10.8, 24.1)
CIS/CIS+Pap	91	60.4 (49.6, 69.6)	36.1 (26.2, 46.1)	19.8 (12.2, 28.8)	14.0 (7.7, 22.1)	11.5 (5.9, 19.3)
CIS Only	59	66.1 (52.5, 76.6)	46.6 (33.3, 58.7)	25.1 (14.7, 36.8)	17.9 (9.2, 28.9)	14.1 (6.5, 24.5)
CIS+Pap	32	50.0 (31.9, 65.7)	23.3 (10.4, 39.2)	10.0 (2.6, 23.5)	6.7 (1.2, 19.1)	6.7 (1.2, 19.1)
Pap Only	38	66.7 (48.8, 79.5)	42.7 (26.1, 58.3)	33.6 (18.5, 49.3)	30.5 (16.1, 46.2)	30.5 (16.1, 46.2)
mITT Population, % (95% CI)						
Overall	105	58.0 (47.9, 66.8)	33.5 (24.6, 42.6)	20.7 (13.5, 29.0)	15.8 (9.5, 23.5)	14.8 (8.7, 22.4)
CIS/CIS+Pap	84	57.1 (45.9, 66.9)	31.2 (21.5, 41.3)	16.2 (9.2, 25.0)	11.2 (5.5, 19.2)	10.0 (4.7, 17.6)
CIS Only	54	63.0 (48.7, 74.3)	41.4 (28.1, 54.3)	19.7 (10.2, 31.5)	13.8 (6.1, 24.7)	NE
CIS+Pap	30	46.7 (28.4, 63.0)	20.0 (8.1, 35.6)	10.0 (2.5, 23.6)	6.7 (1.2, 19.2)	6.7 (1.2, 19.2)
Pap Only	21	61.9 (38.1, 78.8)	42.9 (21.9, 62.3)	38.1 (18.3, 57.8)	33.3 (14.9, 53.1)	33.3 (14.9, 53.1)

CI= confidence interval; CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat; NE = not estimable; Pap = papillary

**Table 31. Kaplan-Meier Estimates of Disease-Free Survival by BCG Failure Type in Study 301 as Assessed by the Central Pathologist**

	N	Number of Months from Baseline				
		3	6	12	18	24
ITT Population, % (95% CI)						
Relapsing	22	77.3 (53.7, 89.8)	53.6 (30.9, 71.8)	39.0 (18.9, 58.6)	NE	NE
Refractory	107	59.2 (49.2, 67.9)	34.8 (25.6, 44.0)	20.4 (13.2, 28.9)	15.3 (9.1, 23.1)	13.2 (7.4, 20.7)
ITT Population – Papillary only, % (95% CI)						
Relapsing	4	75.0 (12.8, 96.1)	75.0 (12.8, 96.1)	NE	NE	NE
Refractory	34	65.6 (46.6, 79.3)	38.3 (21.5, 55.0)	31.4 (16.0, 48.1)	27.9 (13.4, 44.5)	27.9 (13.4, 44.5)
ITT Population – CIS with or without papillary, % (95% CI)						
Relapsing	18	77.8 (51.1, 91.0)	48.5 (24.2, 69.1)	36.4 (15.2, 58.1)	NE	NE
Refractory	73	56.2 (44.1, 66.6)	33.1 (22.5, 44.1)	15.8 (8.5, 25.3)	10.1 (4.4, 18.4)	6.9 (2.4, 14.6)
ITT Population – CIS only, % (95% CI)						
Relapsing	11	72.7 (37.1, 90.3)	62.3 (27.7, 84.0)	51.9 (19.8, 76.7)	NE	NE
Refractory	48	64.6 (49.4, 76.3)	40.9 (26.9, 54.4)	19.4 (9.6, 31.7)	12.9 (5.3, 24.1)	8.1 (2.4, 18.5)
ITT Population – CIS and papillary, % (95% CI)						
Relapsing	7	85.7 (33.4, 97.9)	28.6 (4.1, 61.2)	NE	NE	NE
Refractory	25	40.0 (21.3, 58.1)	17.8 (5.7, 35.3)	8.9 (1.6, 24.5)	4.4 (0.3, 18.5)	4.4 (0.3, 18.5)

**Table 31. Kaplan-Meier Estimates of Disease-Free Survival by BCG Failure Type in Study 301 as Assessed by the Central Pathologist - Continued**

	N	Number of Months from Baseline				
		3	6	12	18	24
mITT Population, % (95% CI)						
Relapsing	20	75.0 (50.0, 88.7)	48.8 (25.7, 68.4)	37.9 (17.3, 58.5)	NE	NE
Refractory	85	54.0 (42.8, 63.9)	30.0 (20.6, 39.9)	16.8 (9.7, 25.5)	12.0 (6.1, 19.9)	10.8 (5.3, 18.5)
mITT Population – Papillary only, % (95% CI)						
Relapsing	2	NE	NE	NE	NE	NE
Refractory	19	63.2 (37.9, 80.4)	42.1 (20.4, 62.5)	36.8 (16.5, 57.5)	31.6 (12.9, 52.2)	31.6 (12.9, 52.2)
mITT Population – CIS with or without papillary, % (95% CI)						
Relapsing	18	77.8 (51.1, 91.0)	48.5 (24.2, 69.1)	36.4 (15.2, 58.1)	NE	NE
Refractory	66	51.5 (38.9, 62.7)	26.5 (16.5, 37.6)	10.9 (4.8, 19.9)	6.2 (2.0, 13.9)	4.7 (1.2, 11.8)
mITT Population – CIS only, % (95% CI)						
Relapsing	11	72.7 (37.1, 90.3)	62.3 (27.7, 84.0)	51.9 (19.8, 76.7)	NE	NE
Refractory	43	60.5 (44.3, 73.3)	33.9 (20.2, 48.1)	12.1 (4.4, 23.9)	7.3 (1.9, 17.7)	NE
mITT Population – CIS and papillary, % (95% CI)						
Relapsing	7	85.7 (33.4, 97.9)	28.6 (4.1, 61.2)	NE	NE	NE
Refractory	23	34.8 (16.6, 53.7)	13.0 (3.3, 29.7)	8.7 (1.5, 24.2)	4.3 (0.3, 18.2)	4.3 (0.3, 18.2)

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat; NE = not estimable

**Table 32. Kaplan-Meier Estimates of Disease-Free Survival by BCG Instillation Group in Study 301**

	N	Number of Months from Baseline				
		3	6	12	18	24
ITT Population, % (95% CI)						
≤ 6 instillations	32	65.5 (46.4, 79.2)	29.5 (14.8, 45.8)	16.4 (6.0, 31.2)	13.1 (4.1, 27.3)	13.1 (4.1, 27.3)
7 - 12 instillations	52	66.7 (51.9, 77.8)	50.0 (35.5, 62.9)	33.3 (20.6, 46.5)	22.9 (12.3, 35.4)	18.5 (9.1, 30.6)
≥ 13 instillations	45	55.6 (40.0, 68.6)	30.4 (17.3, 44.6)	17.8 (7.9, 30.8)	17.8 (7.9, 30.8)	17.8 (7.9, 30.8)
ITT Population – Papillary only, % (95% CI)						
≤ 6 instillations	10	90.0 (47.3, 98.5)	40.0 (12.3, 67.0)	30.0 (7.1, 57.8)	NE	NE
7 - 12 instillations	15	69.2 (37.3, 87.2)	53.8 (24.8, 76.0)	46.2 (19.2, 69.6)	46.2 (19.2, 69.6)	46.2 (19.2, 69.6)
≥ 13 instillations	13	46.2 (19.2, 69.6)	34.6 (10.1, 61.1)	23.1 (4.1, 51.0)	23.1 (4.1, 51.0)	23.1 (4.1, 51.0)
ITT Population – CIS with or without papillary, % (95% CI)						
≤ 6 instillations	22	54.5 (32.1, 72.4)	24.8 (9.2, 44.3)	9.9 (1.7, 27.0)	9.9 (1.7, 27.0)	9.9 (1.7, 27.0)
7 - 12 instillations	37	64.9 (47.3, 77.9)	47.9 (31.1, 62.9)	28.2 (14.9, 43.3)	14.1 (5.2, 27.4)	NE
≥ 13 instillations	32	59.4 (40.5, 74.0)	29.8 (15.0, 46.1)	16.5 (6.1, 31.5)	16.5 (6.1, 31.5)	16.5 (6.1, 31.5)
ITT Population – CIS only, % (95% CI)						
≤ 6 instillations	13	76.9 (44.2, 91.9)	38.5 (14.1, 62.8)	15.4 (2.5, 38.8)	15.4 (2.5, 38.8)	15.4 (2.5, 38.8)
7 - 12 instillations	25	64.0 (42.2, 79.4)	55.5 (34.1, 72.4)	34.1 (16.4, 52.7)	17.1 (5.4, 34.3)	NE
≥ 13 instillations	21	61.9 (38.1, 78.8)	36.1 (16.4, 56.3)	NE	NE	NE
ITT Population – CIS and papillary, % (95% CI)						
≤ 6 instillations	9	22.2 (3.4, 51.3)	NE	NE	NE	NE
7 - 12 instillations	12	66.7 (33.7, 86.0)	33.3 (10.3, 58.8)	16.7 (2.7, 41.3)	NE	NE
≥ 13 instillations	11	54.5 (22.9, 78.0)	18.2 (2.9, 44.2)	9.1 (0.5, 33.3)	9.1 (0.5, 33.3)	9.1 (0.5, 33.3)

**Table 32. Kaplan-Meier Estimates of Disease-Free Survival by BCG Instillation Group in Study 301 - Continued**

	N	Number of Months from Baseline				
		3	6	12	18	24
mITT Population, % (95% CI)						
≤ 6 instillations	27	59.3 (38.6, 75.0)	25.9 (11.5, 43.1)	14.8 (4.7, 30.4)	NE	NE
7 - 12 instillations	43	60.1 (43.9, 73.0)	43.3 (28.2, 57.5)	26.5 (14.3, 40.3)	16.8 (7.4, 29.5)	14.4 (5.9, 26.7)
≥ 13 instillations	35	54.3 (36.6, 69.0)	27.2 (13.7, 42.7)	18.2 (7.4, 32.7)	18.2 (7.4, 32.7)	18.2 (7.4, 32.7)
mITT Population – Papillary only, % (95% CI)						
≤ 6 instillations	8	87.5 (38.7, 98.1)	50.0 (15.2, 77.5)	37.5 (8.7, 67.4)	NE	NE
7 - 12 instillations	9	55.6 (20.4, 80.5)	44.4 (13.6, 71.9)	44.4 (13.6, 71.9)	44.4 (13.6, 71.9)	44.4 (13.6, 71.9)
≥ 13 instillations	4	25.0 (0.9, 66.5)	25.0 (0.9, 66.5)	25.0 (0.9, 66.5)	25.0 (0.9, 66.5)	25.0 (0.9, 66.5)
mITT Population – CIS with or without papillary, % (95% CI)						
≤ 6 instillations	19	47.4 (24.4, 67.3)	15.8 (3.9, 34.9)	NE	NE	NE
7 - 12 instillations	34	61.8 (43.4, 75.7)	43.2 (26.3, 59.1)	21.6 (9.6, 36.8)	9.3 (2.4, 22.0)	NE
≥ 13 instillations	31	58.1 (39.0, 73.1)	27.4 (13.1, 43.9)	17.1 (6.3, 32.5)	17.1 (6.3, 32.5)	17.1 (6.3, 32.5)
mITT Population – CIS only, % (95% CI)						
≤ 6 instillations	11	72.7 (37.1, 90.3)	27.3 (6.5, 53.9)	NE	NE	NE
7 - 12 instillations	22	59.1 (36.1, 76.2)	49.2 (27.3, 68.0)	24.6 (9.1, 44.1)	9.8 (1.7, 26.8)	NE
≥ 13 instillations	21	61.9 (38.1, 78.8)	36.1 (16.4, 56.3)	NE	NE	NE
mITT Population – CIS and papillary, % (95% CI)						
≤ 6 instillations	8	12.5 (0.7, 42.3)	NE	NE	NE	NE
7 - 12 instillations	12	66.7 (33.7, 86.0)	33.3 (10.3, 58.8)	16.7 (2.7, 41.3)	NE	NE
≥ 13 instillations	10	50.0 (18.4, 75.3)	10.0 (0.6, 35.8)	10.0 (0.6, 35.8)	10.0 (0.6, 35.8)	10.0 (0.6, 35.8)

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat; NE = not estimable

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**Table 33. Kaplan-Meier Estimates of Progression-Free Survival by Baseline Tumor Stage in Study 301 as Assessed by the Central Pathologist**

	N	Number of Months from Baseline				
		3	6	12	18	24
<b>ITT Population, % (95% CI)</b>						
Overall	129	100 (100, 100)	92.3 (85.7, 95.9)	85.0 (76.5, 90.6)	80.2 (70.8, 86.9)	75.9 (65.7, 83.5)
CIS/CIS+Pap	91	100 (100, 100)	92.5 (84.0, 96.6)	81.7 (70.3, 89.1)	76.1 (63.6, 84.8)	69.3 (55.5, 79.6)
CIS Only	59	100 (100, 100)	89.1 (77.3, 95.0)	80.4 (66.4, 89.1)	75.4 (60.4, 85.4)	72.1 (56.2, 83.1)
CIS+Pap	32	100 (100, 100)	100 (100, 100)	84.1 (57.7, 94.7)	77.1 (49.0, 91.0)	61.7 (32.6, 81.2)
Pap Only	38	100 (100, 100)	91.9 (76.9, 97.3)	91.9 (76.9, 97.3)	88.5 (72.0, 95.6)	88.5 (72.0, 95.6)
<b>mITT Population, % (95% CI)</b>						
Overall	105	100 (100, 100)	93.6 (86.3, 97.1)	85.6 (75.8, 91.6)	79.4 (68.3, 87.0)	74.0 (61.9, 82.8)
CIS/CIS+Pap	84	100 (100, 100)	91.9 (82.8, 96.3)	81.4 (69.2, 89.1)	75.2 (61.9, 84.5)	67.9 (53.2, 78.8)
CIS Only	54	100 (100, 100)	88.0 (75.2, 94.4)	78.2 (63.0, 87.8)	72.5 (56.2, 83.6)	NE
CIS+Pap	30	100 (100, 100)	100 (100, 100)	88.0 (59.4, 96.9)	80.6 (50.6, 93.4)	64.5 (33.8, 83.8)
Pap Only	21	100 (100, 100)	100 (100, 100)	100 (100, 100)	93.8 (63.2, 99.1)	93.8 (63.2, 99.1)

CI = confidence interval; CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat; NE = not estimable

**Table 34. Kaplan-Meier Estimates of Progression-Free Survival by BCG Failure Type in Study 301 as Assessed by the Central Pathologist**

	N	Number of Months from Baseline				
		3	6	12	18	24
ITT Population, % (95% CI)						
Relapsing	22	100 (100, 100)	90.0 (65.6, 97.4)	NE	NE	NE
Refractory	107	100 (100, 100)	92.7 (85.4, 96.5)	85.2 (75.7, 91.2)	79.4 (68.7, 86.8)	74.1 (62.4, 82.7)
ITT Population – Papillary only, % (95% CI)						
Relapsing	4	NE	NE	NE	NE	NE
Refractory	34	100 (100, 100)	90.9 (74.4, 97.0)	90.9 (74.4, 97.0)	87.1 (69.0, 95.0)	87.1 (69.0, 95.0)
ITT Population – CIS with or without papillary, % (95% CI)						
Relapsing	18	100 (100, 100)	87.5 (58.6, 96.7)	NE	NE	NE
Refractory	73	100 (100, 100)	93.7 (84.2, 97.6)	82.1 (68.9, 90.0)	75.0 (60.4, 84.9)	66.2 (50.0, 78.3)
ITT Population – CIS only, % (95% CI)						
Relapsing	11	100 (100, 100)	NE	NE	NE	NE
Refractory	48	100 (100, 100)	91.2 (78.1, 96.6)	80.6 (64.6, 89.9)	74.4 (57.1, 85.5)	70.3 (51.8, 82.7)
ITT Population – CIS and papillary, % (95% CI)						
Relapsing	7	100 (100, 100)	100 (100, 100)	NE	NE	NE
Refractory	25	100 (100, 100)	100 (100, 100)	85.6 (52.5, 96.3)	76.1 (41.4, 91.8)	54.3 (21.3, 78.6)

**Table 34. Kaplan-Meier Estimates of Progression-Free Survival by BCG Failure Type in Study 301 as Assessed by the Central Pathologist - Continued**

	Number of Months from Baseline					
	N	3	6	12	18	24
mITT Population, % (95% CI)						
Relapsing	20	100 (100, 100)	88.9 (62.4, 97.1)	NE	NE	NE
Refractory	85	100 (100, 100)	94.7 (86.6, 98.0)	86.3 (75.2, 92.7)	78.8 (66.0, 87.2)	72.1 (58.0, 82.1)
mITT Population – Papillary only, % (95% CI)						
Relapsing	2	NE	NE	NE	NE	NE
Refractory	19	100 (100, 100)	100 (100, 100)	100 (100, 100)	93.3 (61.3, 99.0)	93.3 (61.3, 99.0)
mITT Population – CIS with or without papillary, % (95% CI)						
Relapsing	18	100 (100, 100)	87.5 (58.6, 96.7)	NE	NE	NE
Refractory	66	100 (100, 100)	93.1 (82.6, 97.4)	81.6 (67.2, 90.2)	73.6 (57.7, 84.4)	63.9 (46.4, 77.0)
mITT Population – CIS only, % (95% CI)						
Relapsing	11	100 (100, 100)	NE	NE	NE	NE
Refractory	43	100 (100, 100)	90.1 (75.6, 96.1)	77.8 (60.0, 88.4)	70.6 (51.5, 83.3)	NE
mITT Population – CIS and papillary, % (95% CI)						
Relapsing	7	100 (100, 100)	100 (100, 100)	NE	NE	NE
Refractory	23	100 (100, 100)	100 (100, 100)	90.9 (50.8, 98.7)	80.8 (42.3, 94.9)	57.7 (22.1, 81.9)

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat; NE = not estimable

**Table 35. Kaplan-Meier Estimates of Progression-Free Survival by BCG Instillation Group in Study 301 as Assessed by the Central Pathologist**

	N	Number of Months from Baseline				
		3	6	12	18	24
ITT Population, % (95% CI)						
≤ 6 instillations	32	100 (100, 100)	92.7 (73.9, 98.1)	84.3 (63.2, 93.8)	79.9 (58.0, 91.1)	68.4 (44.1, 83.9)
7 - 12 instillations	52	100 (100, 100)	90.0 (77.6, 95.7)	85.4 (71.7, 92.8)	77.7 (62.2, 87.4)	74.8 (58.8, 85.4)
≥ 13 instillations	45	100 (100, 100)	95.0 (81.3, 98.7)	85.8 (68.9, 93.9)	85.8 (68.9, 93.9)	85.8 (68.9, 93.9)
ITT Population – Papillary only, % (95% CI)						
≤ 6 instillations	10	100 (100, 100)	NE	NE	NE	NE
7 - 12 instillations	15	100 (100, 100)	93.3 (61.3, 99.0)	93.3 (61.3, 99.0)	86.2 (55.0, 96.4)	86.2 (55.0, 96.4)
≥ 13 instillations	13	100 (100, 100)	91.7 (53.9, 98.8)	91.7 (53.9, 98.8)	91.7 (53.9, 98.8)	91.7 (53.9, 98.8)
ITT Population – CIS with or without papillary, % (95% CI)						
≤ 6 instillations	22	100 (100, 100)	94.4 (66.6, 99.2)	81.0 (51.6, 93.5)	73.6 (43.6, 89.3)	52.6 (21.6, 76.4)
7 - 12 instillations	37	100 (100, 100)	88.6 (72.4, 95.5)	81.6 (63.3, 91.4)	73.7 (53.6, 86.1)	68.7 (47.5, 82.8)
≥ 13 instillations	32	100 (100, 100)	96.4 (77.2, 99.5)	NE	NE	NE
ITT Population – CIS only, % (95% CI)						
≤ 6 instillations	13	100 (100, 100)	92.3 (56.6, 98.9)	73.8 (38.5, 90.8)	73.8 (38.5, 90.8)	61.5 (25.8, 84.0)
7 - 12 instillations	25	100 (100, 100)	83.3 (61.5, 93.4)	79.2 (57.0, 90.8)	NE	NE
≥ 13 instillations	21	100 (100, 100)	94.7 (68.1, 99.2)	NE	NE	NE
ITT Population – CIS and papillary, % (95% CI)						
≤ 6 instillations	9	100 (100, 100)	100 (100, 100)	100 (100, 100)	66.7 (5.4, 94.5)	NE
7 - 12 instillations	12	100 (100, 100)	100 (100, 100)	87.5 (38.7, 98.1)	87.5 (38.7, 98.1)	75.0 (31.5, 93.1)
≥ 13 instillations	11	100 (100, 100)	100 (100, 100)	NE	NE	NE

**Table 35. Kaplan-Meier Estimates of Progression-Free Survival by BCG Instillation Group in Study 301 as Assessed by the Central Pathologist - Continued**

	N	Number of Months from Baseline				
		3	6	12	18	24
mITT Population, % (95% CI)						
≤ 6 instillations	27	100 (100, 100)	95.8 (73.9, 99.4)	85.7 (61.8, 95.2)	80.4 (55.6, 92.2)	NE
7 - 12 instillations	43	100 (100, 100)	90.2 (76.1, 96.2)	84.4 (68.3, 92.7)	74.7 (56.6, 86.1)	70.9 (52.2, 83.4)
≥ 13 instillations	35	100 (100, 100)	96.7 (78.6, 99.5)	NE	NE	NE
mITT Population – Papillary only, % (95% CI)						
≤ 6 instillations	8	NE	NE	NE	NE	NE
7 - 12 instillations	9	100 (100, 100)	100 (100, 100)	100 (100, 100)	87.5 (38.7, 98.1)	87.5 (38.7, 98.1)
≥ 13 instillations	4	NE	NE	NE	NE	NE
mITT Population – CIS with or without papillary, % (95% CI)						
≤ 6 instillations	19	100 (100, 100)	93.8 (63.2, 99.1)	78.1 (46.0, 92.5)	69.4 (37.1, 87.5)	NE
7 - 12 instillations	34	100 (100, 100)	87.5 (70.0, 95.1)	79.7 (59.9, 90.5)	70.9 (49.4, 84.5)	65.4 (42.9, 80.8)
≥ 13 instillations	31	100 (100, 100)	96.3 (76.5, 99.5)	NE	NE	NE
mITT Population – CIS only, % (95% CI)						
≤ 6 instillations	11	100 (100, 100)	90.9 (50.8, 98.7)	68.2 (29.7, 88.6)	68.2 (29.7, 88.6)	NE
7 - 12 instillations	22	100 (100, 100)	81.0 (56.9, 92.4)	76.2 (51.9, 89.3)	NE	NE
≥ 13 instillations	21	100 (100, 100)	94.7 (68.1, 99.2)	NE	NE	NE
mITT Population – CIS and papillary, % (95% CI)						
≤ 6 instillations	8	100 (100, 100)	100 (100, 100)	100 (100, 100)	66.7 (5.4, 94.5)	NE
7 - 12 instillations	12	100 (100, 100)	100 (100, 100)	87.5 (38.7, 98.1)	87.5 (38.7, 98.1)	75.0 (31.5, 93.1)
≥ 13 instillations	10	100 (100, 100)	100 (100, 100)	NE	NE	NE

BCG = bacillus Calmette-Guérin; CI = confidence interval; CIS = carcinoma *in situ*; ITT = intent-to-treat; mITT = modified intent-to-treat; NE = not estimable

**17 SUBJECT DEATHS IN STUDY 301**

**Table 36. Subject Deaths in Study 301**

<b>Subject Number</b>	<b>Date of First Dose</b>	<b>Date of Last Dose</b>	<b>Date of Death (Study Day)</b>	<b>Primary Cause of Death</b>
<b>Deaths On-Treatment (n=4)</b>				
1-102-01	29 Jun 2007	03 Jul 2008	(b) (6)	Cerebral haematoma
1-103-03	15 Oct 2007	26 Nov 2007	(b) (6)	Multi-organ failure
1-114-09	19 Feb 2009	26 Mar 2009	(b) (6)	Pulmonary fibrosis
1-117-01	17 Jun 2008	11 Aug 2009	(b) (6)	Cardio-respiratory arrest
<b>Deaths During Follow-Up Phase (n=23)</b>				
1-003-09	13 Nov 2008	11 Aug 2009	(b) (6)	Non-bladder malignant tumor
1-004-03	16 Jun 2008	17 Nov 2008	(b) (6)	Other: most responsible diagnosis: bladder cancer; uneventful course of palliative care
1-004-07	18 Feb 2009	27 Oct 2010	(b) (6)	Cardiovascular disease
1-005-05	24 Feb 2009	08 Sep 2009	(b) (6)	Invasive bladder cancer
1-007-03	18 May 2007	19 May 2009	(b) (6)	Unknown
1-007-04	04 Jul 2007	21 Jan 2008	(b) (6)	Other: bladder cancer with liver and bone metastases
1-007-07	07 Aug 2008	04 Feb 2009	(b) (6)	Other: lung cancer
1-100-04	12 Dec 2007	16 Jan 2008	(b) (6)	Invasive bladder cancer
1-100-05	29 May 2008	17 Dec 2008	(b) (6)	Other: acute on chronic respiratory failure
1-103-05	19 Nov 2007	03 Mar 2008	(b) (6)	Invasive bladder cancer
1-103-06	17 Jan 2008	15 May 2008	(b) (6)	Unknown
1-103-09	13 May 2008	09 Sep 2008	(b) (6)	Other: pancreatic cancer with metastasis to lung
1-103-15	06 Apr 2009	31 Aug 2009	(b) (6)	Unknown
1-104-04	17 Apr 2007	21 Apr 2009	(b) (6)	Cardiovascular disease
1-105-06	18 Dec 2007	25 Mar 2008	(b) (6)	Unknown

**Table 36. Subject Deaths in Study 301 - Continued**

<b>Subject Number</b>	<b>Date of First Dose</b>	<b>Date of Last Dose</b>	<b>Date of Death (Study Day)</b>	<b>Primary Cause of Death</b>
1-105-09	06 May 2008	10 Jun 2008	(b) (6)	Other: acute respiratory failure superimposed on multi-organ failure
1-106-05	17 Apr 2008	15 Oct 2008	(b) (6)	Other: perforated bowel with resultant multi-organ system failure including respiratory failure, severe hypotension refractory to presser support, renal failure and sepsis syndrome
1-107-02	10 Jul 2008	29 Oct 2008	(b) (6)	Invasive bladder cancer
1-112-05	24 Feb 2009	30 Jul 2009	(b) (6)	Cardiovascular disease
1-115-03	19 Dec 2008	23 Apr 2009	(b) (6)	Unknown
1-116-01	27 May 2008	02 Sep 2008	(b) (6)	Cardiovascular disease
1-116-02	22 May 2008	03 Sep 2008	(b) (6)	Invasive bladder cancer
1-119-02	18 Sep 2008	21 Jan 2009	(b) (6)	Other: primary cause is colon cancer; secondary bladder cancer
<b>Death Following Study Completion (n=1)</b>				
1-102-02	24 Jul 2007	16 Nov 2007	(b) (6)	Other: metastatic bladder cancer