SYNOPSIS

Clinical Study Report EN3348-303

TITLE OF STUDY:

A Phase 3, randomized, active-controlled, open-label, multicenter study to evaluate the efficacy and safety of EN3348 (MCC) as compared with mitomycin C in the intravesical treatment of subjects with BCG recurrent or refractory non-muscle invasive bladder cancer

INVESTIGATORS AND STUDY CENTERS:

The study was to be conducted in approximately 150 investigational sites worldwide. Due to enrollment difficulties, study EN3348-303 was discontinued on November 2, 2012. At the time the study was stopped, the randomized subjects were recruited in 41 recruiting sites among the 88 initiated sites located in the United States (68 sites; 64 subjects), Canada (12 sites; 19 subjects), Poland (4 sites; 1 subject), the United Kingdom (2 sites; no subject), Germany (1 site; no subject), and the Netherlands (1 site; no subject).

PUBLICATIONS:	None	
STUDY PERIOD:	Date first patient enrolled:	16-Feb-2011
	Date last patient completed:	04-Jan-2013
	Date of early termination:	02-Nov-2012
CLINICAL PHASE:	Phase 3	

OBJECTIVES:

The overall objective of this study was to determine the efficacy and safety of intravesical mycobacterial cell wall-nucleic acid complex (MCNA) suspension as compared with mitomycin C in the treatment of subjects with Bacillus Calmette-Guérin (BCG) recurrent or refractory non-muscle invasive bladder cancer (NMIBC). MCNA suspension was previously known as mycobacterial cell wall-DNA complex (MCC) suspension.

As discussed in the main clinical study report (CSR) EN3348-303 document (section Changes in the Conduct of the Analysis), study EN3348-303 was discontinued early. Thus, the planned analysis as stated in the protocol was not performed. Instead, the analysis was mainly descriptive focusing on summarizing the safety findings in the safety population, with a very limited summary on efficacy.

Primary Objectives:

The primary objective of the study was to determine the efficacy of intravesical MCNA suspension as compared with mitomycin C in the treatment of subjects with BCG recurrent or refractory NMIBC.

As originally planned in the protocol, the primary efficacy variable was the event-free survival defined as the interval from randomization to documented tumor recurrence, tumor progression to muscle invasive bladder cancer or death for any cause, whichever occurred first.

Secondary efficacy variables were:

- The event-free survival rate at 1 and 2 years;
- The recurrence rate at 1 and 2 years;
- The progression rate at 1 and 2 years;
- The time to cystectomy, and;
- The overall survival (OS).

Secondary Objectives:

The secondary objective was to determine the safety of intravesical MCNA suspension as compared with mitomycin C in the treatment of subjects with BCG recurrent or refractory NMIBC.

Assessment of safety was based on the incidence of adverse events (AEs) and abnormal findings in clinical laboratory values, vital signs, and physical examinations.

METHODOLOGY:

This was a phase 3 randomized, active-controlled, open-label, multicenter study evaluating the efficacy and safety of MCNA suspension as compared with mitomycin C in the treatment of subjects with BCG recurrent or refractory NMIBC. Subjects with either recurrent or refractory NMIBC (Ta high grade (HG), T1 low or high grade, carcinoma *in situ* [CIS]) were eligible for participation in this study.

The study was divided into 4 phases: screening, induction, maintenance, and follow-up and was to be conducted over 3 years. The screening phase lasted up to 8 weeks, with a possible extension to 12 weeks if a re-transurethral resection of a bladder tumor (re-TURBT) was necessary to obtain tissue from the muscularis propria for T1 papillary disease. The induction phase consisted of the first 6 weeks of the study, during which subjects 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 (until month 36/end of study), with a variable duration dependent upon when the subject was entering (randomized into) the study.

During the screening phase, subjects were evaluated for study enrollment by review of inclusion and exclusion criteria. Procedures associated with standard of care for the assessment of bladder cancer preceded subject signing of the informed consent. The procedures included an extravesical workup performed per institutional process as part of standard of care within 6 months prior to randomization and indicating no malignancy in the upper or lower extravesical urinary tract. The procedures included also a urine cytology, cystoscopy, and TURBT/biopsy that had to be completed within 8 weeks prior to randomization. Investigators were asked to make every effort to obtain tissue from the muscularis propria when resecting papillary tumors, and not fulgurate tumors until adequate biopsy samples had been obtained. The investigators were then to send the

biopsy samples to the local pathologist to determine if the subject had a qualifying diagnosis. If the local pathology results indicated a diagnosis of high grade NMIBC, the subject was invited to be screened for potential participation in the study, upon which the subject then signed the informed consent and was assigned a unique subject number. From that point, all biopsy samples were to be sent to the central pathologist and all remaining screening phase assessments were to be completed.

The induction phase covered a period of 6 weeks. During this time, subjects were to receive 6 weekly intravesical instillations of either 8 mg MCNA suspension or 40 mg mitomycin C via a transurethral catheter. At month 3, subjects were to be evaluated to assure the disease had not progressed. Evaluations consisted of standard cystoscopy examination and voided urine cytology. If either evaluation showed evidence of suspicious or evident tumors, then a TURBT/biopsy was to be performed and analyzed by the central pathologist. Subjects 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. Subjects that showed evidence of high grade Ta, T1 (evidence of tissue from the muscularis propria was required) or muscle invasive bladder cancer (MIBC) were to be discontinued from further study treatment and entered the follow-up phase.

The maintenance phase lasted from months 3 to 12. During this time, subjects received monthly instillations with the study drug to which they were randomized for up to an additional 10 doses. Subsequent to the month 3 evaluation, efficacy evaluations were to be performed every 3 months at months 6, 9, and 12. Evaluations included a standard cystoscopy examination and voided urine cytology. TURBTs and biopsies were to be performed if either cytology or cystoscopy was positive, except at month 6 where mandatory (see below). Evidence of tissue from the muscularis propria was required to be present in the sample (for papillary tumors only). If at any time during the maintenance phase a subject presented with symptoms associated with possible recurrence or progression, the subject's disease status was to be evaluated per the institution's standard process. At the month 6 evaluations, mandatory biopsies were to be performed for all subjects, regardless of cytology or cystoscopy results.

At month 6 and thereafter at each evaluation visit, all subjects were to be evaluated and managed according to the following results:

- Subjects who were not tumor-free, i.e., with evidence of papillary lesions, CIS or progression to T2 were withdrawn from further study treatment and entered the follow-up phase.
- Subjects who were tumor-free continued on maintenance treatment.

If at any time during the course of the study, the urine cytology was positive and the TURBT/biopsy results were negative, the investigator was to evaluate the subject for extravesical disease.

Subjects entered the follow-up phase after completing or early discontinuation of the maintenance phase. The follow-up phase was to last a maximum of 24 months (until month 36/end of study), with a variable duration dependent upon when the subject was entering (randomized into) the study. During this phase, evaluations were to be performed every 3 months for the first year of follow-up and every 6 months thereafter to end of study. Evaluations were comprised of cystoscopy and urine cytology while TURBT and bladder biopsies were to be done

only when indicated. During this phase, data on disease recurrence, progression to muscle invasive disease, secondary malignancy, cystectomy, additional anti-cancer therapies, and overall survival were to be collected.

All randomized subjects, regardless of number of study drug instillations received, were to be followed until the end of study (EOS), defined as 12 months after the last subject had been randomized or 282 events had occurred, whichever occurred later, or the time when the Sponsor terminated the study. For an individual subject, the EOS could be achieved by completing all required assessments through the termination of the trial or earlier due to early discontinuation or withdrawal of informed consent.

Safety was monitored on an ongoing basis during the study by an independent monitoring committee through AEs, physical examinations, and abnormal laboratory test results. In addition, vital signs were captured, and monitored for abnormalities or aberrant values.

NUMBER OF SUBJECTS (planned and analyzed):

Approximately 450 subjects were planned to be randomized. The intended randomization was 1:1 and stratified by geographic region (North America, India (planned), Europe), tumor pathology (CIS versus no CIS), prior BCG response (refractory versus recurrent), and prior intravesical chemotherapy (yes/no).

Due to enrollment difficulties, study EN3348-303 was discontinued on November 2, 2012. The decision to discontinue the clinical study was based solely on logistical issues and was not due to any efficacy or safety-related issue. The number of subjects randomized at time of closure was 84, representing less than 20% of the planned enrollment.

Among the 84 subjects included in the intent-to-treat (ITT) population, 39 subjects were randomized to MCNA suspension (MCC treatment group) and 45 to mitomycin C. Two subjects in the ITT population (MCC treatment group) were excluded from the safety population since they never received any dose of the study medication. Thus, the safety population consisted of 37 subjects on MCNA suspension and 45 subjects on mitomycin C for a total of 82 subjects.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

For inclusion into the study, subjects were required to fulfill all of the following main criteria:

- Males and females who are 18 years of age or older at time of consent signing
- Have either BCG recurrent or refractory NMIBC:
  - 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[1] with or without maintenance/re-treatment at 3 months
  - Recurrent disease was defined as reappearance of disease after achieving a tumor-free status by 6 months following a full induction course of BCG[1] with or without maintenance/re-treatment at 3 months. Subjects with recurrent disease must have recurred within 18 months following the last dose of BCG.

[1]A full induction course of BCG is defined as at least 5 out of 6 total expected instillations of BCG within a period of 2 months, regardless of dose strength.

- Have histologically confirmed NMIBC (according to 2004 World Health Organization (WHO) classification) within 8 weeks prior to randomization:
  - High grade Ta papillary lesion(s)
  - High or low grade T1 papillary lesion(s) (biopsy sample must include evidence of muscularis propria)
  - CIS, with or without Ta or T1 papillary tumor(s) of any grade
- Have had all visible papillary and resectable CIS lesion(s) removed by TURBT within 8 weeks prior to randomization
- Available for the duration of the study including follow-up (approximately 36 months)
- Have an Eastern Cooperative Oncology Group (ECOG) performance status grade of 2 or less
- 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
- 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
- Is able to understand and give written informed consent

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION, BATCH NUMBERS:

MCNA suspension (total of 8 mL) was reconstituted in 42 mL of sterile water for injection (WFI), for a total instillate volume of 50 mL. MCNA suspension was administered at a dose of 8 mg intravesically by an experienced health care professional. The lot numbers of MCNA suspension used in this study were M10JA02, M11JA03, and M11JA04.

DURATION OF TREATMENT:

Overall, the study was to be conducted over 3 years. The first subject enrolled was to be on the study for approximately 3 years (i.e., 1 year of treatment and 2 years of follow-up), whereas the last subject enrolled was to be on the study for approximately 1 year (no follow-up).

At the time of study closure notification, subjects in the induction phase were allowed to continue receiving treatment per protocol until completion of the 6-week treatment phase; subjects in the maintenance phase were allowed to continue monthly treatment until December 31, 2012. The last subject last dose was administered on January 4, 2013. All subjects were

followed for adverse events for 30 days after their final study drug instillation, and close-out activities were completed in March 2013.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBERS:

The comparator, mitomycin C (total of 40 mg), was reconstituted with sterile WFI to a total volume of 40 mL. It was prepared and administered intravesically via transurethral catheter per institution practice. The reported batch numbers of mitomycin C used in this study were 01092012-19, 01262012, 02092012, 02102012, 02142012-102, 03282012@59, 04052012, 04262012, 04302012, 05172012, 05182012@62, 06212011, 06212011-16, 06489, 06489, 07232012@79, 07272011, 1024201, 10242011, 11082011, 11172011@56, 12052011, 12062011@78, 12082011, 12132011, 12152011, 12212011, 1390435, 2005259, 1856851, 1864820, 1856857, 1864820, 1895907, 19116787, 1916787, 1916797, 191687, 2005259, 04276, 1864818, 295AJ601, 30292012@108, BF081A, CE008A, CE008A & GE016A, CEC08A, GE016A, GE016A & CE008A, GE016A + IEOS2A, HF020A, ID036A, IE052A, JE099B, L01885, L03066, L11504, M01564, M0405, M04922, M06085, M06085, M06085, M06085, M06490, M06490, M06085, M07852/M08597, M08597/M07852, M08595, M12737, M12737 & M12738, M12738, OT1115-10, PN00097, PN00097 AND N02107, PN00218, PN00218, PN00387, PN003873, PN00526, and Unknown. A listing of subjects receiving each study drug from specific batches is included in Appendix 16.1.6 of the CSR EN3348-303.

CRITERIA FOR EVALUATION:

Efficacy:

The efficacy analysis was to be conducted using the ITT population (i.e., all randomized subjects).

The planned primary efficacy endpoint of this study was the 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, the recurrence rate at 1 and 2 years, the progression rate at 1 and 2 years, the time to cystectomy and the overall survival. However, as mentioned in the main CSR EN3348-303 document (section 9.8.2), the primary and secondary efficacy endpoints were not evaluated due to enrollment difficulties which resulted in early study termination.

Instead, the assessments included descriptive statistics of standard cystoscopy, urine cytology and bladder tumor pathology assessments by local and central pathologists.

Safety:

Safety assessments included adverse events, vital signs, clinical laboratory, physical examinations, and other safety observations such as prior and concomitant medications, second primary cancers, and concomitant bladder cancer therapies. All concomitant medication was coded using the WHO Drug Dictionary (version Mar 2010 B2). Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 dictionary.

Treatment-emergent adverse events (TEAEs) (i.e., those events that start on/or after the first instillation of the study medication and within 30 days after the last instillation of the study medication) were tabulated. Adverse events were captured from the time of signing the informed consent through 30 days following the last dose of study drug. Any serious adverse event (SAE) that was felt by the investigator to be related to the study medication had to be reported regardless of the amount of time since the last dose received.

STATISTICAL METHODS:

As mentioned above, due to enrollment difficulties, study EN3348-303 was discontinued early. The number of subjects randomized at the time of closure represented less than 20% of the planned enrollment of 450 subjects. Thus, the planned analysis as stated in the protocol was not performed. Instead, the analysis described in the revised statistical analysis plan (SAP) has mainly focused on the safety summary with very limited summary on efficacy, specifically the description of standard cystoscopy, urine cytology results, and bladder tumor pathology.

Unless otherwise specified, continuous data were summarized using descriptive statistics (i.e., number of subjects, mean, standard deviation (SD), median, minimum, maximum), while categorical data were tabulated in terms of counts and percentages (or proportions). Missing data were not imputed and were reported as missing.

Assessment of safety was based on the incidence of AEs, AEs resulting in treatment delay and those resulting in discontinuation from treatment, and SAEs. AE summaries were provided showing the number and percentage of subjects who experienced at least 1 AE. These summaries were presented by system organ class (SOC) and preferred term (PT).

Laboratory data and change from baseline were summarized using descriptive statistics. Shift tables summarizing change from baseline to post-baseline visits were also presented (e.g., normal to high, normal to low). Vital signs, including the change from baseline, and physical examination abnormal findings were also summarized.

The following populations were used for analysis in this study:

- Safety population: all subjects who received at least 1 dose of study medication. All of the safety analysis was performed using this population.
- Intent-to-treat (ITT) population: all subjects who were randomized. In this population, subjects were classified to MCNA (indicated as MCC in tables and listings) or mitomycin C based on the treatment they were randomized to, regardless of which treatment they actually received. Demographics and efficacy outcome summaries were performed using this population.

SUMMARY:

Efficacy results:

Cystoscopy results: The proportion of subjects in the MCC 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. Similarly, the proportion of subjects 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. At screening and at month 3, papillary tumor resection was comparable between both treatment groups and was done in 67.6% and 15.0% of subjects in the MCC group, and 61.8% and 11.1% of subjects in the mitomycin C group, respectively. At 6 months, visualization of a CIS/papillary tumor (MCC: 25.0%; mitomycin C: 22.7%) and papillary tumor resection (MCC: 14.3%; mitomycin C: 18.8%) were comparable between the two treatment groups. A very small number of subjects had available cystoscopical data after 6 months. Overall, from screening to month 6, percentages of visualized CIS and/or papillary tumors and resection of papillary tumors decreased in both treatment groups.

Urine cytology results: At screening, the results of urine cytology were negative for 48.7% of the subjects in the MCC treatment group and 34.1% of subjects in the mitomycin C group, while the proportion of subjects with suspicious results was 5.1% in the MCC group and 22.7% in the mitomycin C group. At screening, the presence of malignant or atypical disease was comparable between the two groups. At month 3, the results for negative and suspicious urine cytology were comparable between both treatment groups, but were higher for malignant cytology in the mitomycin C group (12.5% versus 3.6% for MCC) and higher for atypical cytology in the MCC 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 subjects in the MCC and mitomycin C group, respectively, having negative cytology results. Overall, from screening to month 6, percentages of negative cytology results increased in both treatment groups.

Bladder tumor pathology results: Central pathology results at screening were, in general, comparable between the two treatment groups with 48.7% of subjects in the MCC group and 53.3% of the mitomycin C group having CIS. Among subjects still on study at 6 months, 41.7% and 68.8% of subjects in the MCC and mitomycin C group, respectively, had T0 stage and 2 subjects in the MCC group had low grade disease.

Safety results:

Extent of exposure: All subjects in the safety population were exposed to at least one dose of study treatment. The median duration of MCC treatment was 92 days during which subjects received a median of 7 instillations (range: 3 to 16 instillations), representing a median overall compliance rate of 90.0 % (range: 46.2 to 100.0%). The median duration of mitomycin C treatment was 153 days during which subjects received a median of 8 instillations (range: 5 to 16 instillations), representing a median overall compliance rate of 100.0 % (range: 60.0 to 100.0%).

Among the ITT population, there were 35 (89.7%) and 42 (93.3%) subjects who completed all planned doses of the induction phase within the MCC and mitomycin C treatment groups, respectively. At month 3, there were 20 (51.3%) and 28 (62.2%) subjects who completed all planned doses of this specific period within the MCC and mitomycin C treatment groups, respectively. At month 6, there were 10 (25.6%) and 19 (42.2%) subjects who completed all planned doses of this time-point within the MCC and mitomycin C treatment groups, respectively. In the context of an early discontinued study, the number of subjects who completed all planned doses in all other remaining treatment periods continued to decrease in both treatment groups, with 2 (5.1%) and 4 (8.9%) subjects who completed all planned doses at the end of the maintenance phase (i.e., at month 12) within the MCC and the mitomycin C treatment groups, respectively.

Adverse events and other observations related to safety: There were 32 (86.5%) subjects on MCC and 35 (77.8%) subjects on mitomycin C who had at least one TEAE. A total of 144 and 155 TEAEs were reported for the MCC and mitomycin C subjects, respectively. None of the TEAEs led to study drug withdrawal. However, 12 TEAEs in 7 (18.9%) subjects on MCC and 15 TEAEs in 8 (17.8%) subjects on mitomycin C led to study medication dose delay. In the MCC treatment group, the most common TEAEs were dysuria (9 subjects; 24.3%), haematuria (7 subjects; 18.9%), pollakiuria (6 subjects; 16.2%), fatigue (6 subjects; 16.2%) and urinary tract infection (5 subjects; 13.5%). In the mitomycin C treatment group, the most common TEAEs were dysuria (12 subjects; 26.7%), pollakiuria (6 subjects; 13.3%) and urinary tract infection (5 subjects; 11.1%).

Most subjects had adverse events whose maximum intensity was mild (Grade 1) (16 subjects (43.2%) treated with MCC and 18 subjects (40.0%) treated with mitomycin C) or moderate (Grade 2) (14 subjects (37.8%) treated with MCC and 16 subjects (35.6%) treated with mitomycin C).

Among subjects treated with MCC, the most frequently reported drug-related TEAEs were dysuria experienced by 8 (21.6%) subjects and fatigue experienced by 5 (13.5%) subjects. Among subjects treated with mitomycin C, the most frequently reported drug-related TEAEs were dysuria experienced by 9 (20.0%) subjects and pollakiuria experienced by 4 (8.8%) subjects.

A total of 7 treatment-emergent SAEs were experienced by 4 subjects. Two subjects (2; 5.4%) treated with MCC experienced 4 treatment-emergent SAEs (international normalized ratio (INR) for blood clotting increased, bladder spasm, acute renal failure and asthma) and two subjects (2; 4.4%) treated with mitomycin C experienced 3 treatment-emergent SAEs (cellulitis, sepsis and phlebitis). None of the TEAEs led to study discontinuation or death, and none of the treatment-emergent SAEs experienced by the subjects on MCC were related to the study medication, while an event of phlebitis experienced by one subject on mitomycin C was deemed possibly related to the study medication.

No clinically relevant changes were seen in hematology, chemistry, or urinalysis parameters, vital signs, or physical examinations.

CONCLUSIONS:

The early termination of the study due to enrollment difficulties does not allow for valid conclusions regarding the efficacy of the two treatments and their comparison. Overall, MCNA suspension was well-tolerated. The majority of adverse events were mild or moderate in severity, no adverse events led to study discontinuation or to death, and no treatment-emergent adverse events led to study drug withdrawal. The safety and tolerability profile of MCNA suspension was generally similar to that of mitomycin C. The overall good safety and tolerability profile of MCNA suspension observed in the current study and the potential benefits shown in the previous trials warrant further assessment of its efficacy.

DATE OF REPORT: 21-Feb-2014