PROTOCOL NUMBER CMS-005

PHASE I STUDY OF AD5 [E1-, E2B-]-HER2/NEU VACCINE (ETBX-021) IN SUBJECTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC HER2-EXPRESSING BREAST CANCER

IND Number:	016,871
Principal Investigator:	Hatem Soliman, MD Moffitt Cancer Center 12902 Magnolia Drive Tampa, Florida 33612 Email: hatem.soliman@moffitt.org Office Phone: 813-745-4933
Clinical Study Sponsor:	NantBioScience, Inc.
Sponsor Contact: **(For medical questions/emergencies)**	Wayne R. Godfrey, MD Chief Medical Officer Medical and Safety Monitor Email: wayne@etubics.com Office Phone: 206-838-5110, Ext 9 Mobile Phone: 650-521-2770
Sponsor Contact: **(For study administration, operations, and execution questions)**	Jackie Imm, BA Clinical Trial Manager Email: Jackie.Imm@NantBio.com Office Phone: 919-694-6315
SAE Reporting:	Submit SAE Reports to one (1) of the following: SAE Email: SAE.Reporting@NantBio.com Fax: 800-853-3497

Protocol Version	Date
Original Protocol CMS-005	26 February 2016

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantBioScience, Inc.

Name of Investigational Product:
Ad5 [E1-, E2b-]-HER2/neu Vaccine, Suspension for Injection (ETBX-021)

Name of Active Ingredient:
Ad5 [E1-, E2b-]-HER2/neu

Title of Study:
Phase I Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-Expressing Breast Cancer

Study Number:
CMS-005

Study Phase:
Phase I

Primary Objectives:

- Determine the overall safety and recommended phase 2 dose of ETBX-021 when administered subcutaneously (SC) every 3 weeks for three injections followed by three booster injections at 3-month intervals to subjects with HER2-expressing breast cancer.

Secondary Objectives:

- Make preliminary assessments of objective response rate (ORR), disease control rate (DCR), duration of response, progression-free survival (PFS), and overall survival (OS) in subjects with HER2-expressing breast cancer treated with ETBX-021.

Exploratory Objectives:

- Evaluate the immunogenicity of ETBX-021 and determine the genomic and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

Primary Endpoints:

- Dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) or highest tested dose (HTD).
- Treatment-emergent adverse event (AEs) and serious adverse events (SAEs).
- Clinically significant changes in safety laboratory tests, physical examinations, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), and vital signs.

Secondary Endpoints:

- ORR (confirmed complete or partial response) according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- DCR (confirmed response or stable disease lasting for at least 6 months).
- Duration of response.
- PFS.
- OS.

Exploratory Endpoints:

- Immunogenicity of ETBX-021 by flow cytometric analysis of T-cell frequency, activation status, cytokine profiles, and antibody levels.
- Genetic and proteomic profiling and correlates with efficacy.

Study Design:

This is a Phase I trial in subjects with unresectable locally advanced or metastatic HER2-low expressing (IHC 1+ or 2+) breast cancer. The study will be conducted in two parts: the first part will involve dose escalation using a 3 + 3 design, and the second part will involve the expansion of the MTD or HTD to further evaluate safety, preliminary efficacy, and immunogenicity. In the first part, 3 to 6 subjects will be sequentially enrolled starting at dose cohort 1. Subjects will be assessed for dose-limiting toxicities (DLTs).

- Cohort 1: 5×10^{10} virus particles (VP).
- Cohort 2: 5×10^{11} VP.
- If needed, dose de-escalation cohort (cohort -1): 5×10^{9} VP.

Dose expansion will occur when the MTD or HTD has been determined. An additional 12 subjects will be enrolled in the dose expansion component of the trial, for a total of 18 subjects at the MTD or HTD.

Enrollment (planned):

Up to 30 subjects will be enrolled in the study. In the dose escalation component, 3 to 6 subjects will be sequentially enrolled starting at Cohort 1. In the dose expansion component (i.e., once the MTD or HTD has been identified), an additional 12 subjects will be enrolled for a total of 18 subjects in the MTD/HTD cohort to obtain further safety, preliminary efficacy, and immunogenicity data.

Diagnosis and Main Criteria for Inclusion:

Subjects must have histologically confirmed unresectable locally advanced or metastatic breast cancer that expresses HER2 (IHC 1+ or 2+). Subjects with HER2 IHC 3+ tumors are excluded.

Investigational Product, Dosage, and Mode of Administration:

ETBX-021 (5×10^{9}, 5×10^{10}, or 5×10^{11} VP in 1.0 mL) will be administered by SC injection every 3 weeks for 3 injections, followed by 3 booster injections at 3-month intervals.

Duration of Treatment:

Subjects will receive treatment for up to 42 weeks (injections at 0, 3, and 6 weeks with booster injections at 18, 30, and 42 weeks) or until they experience progressive disease or unacceptable toxicity, withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety: Safety endpoints include assessments of DLT, MTD or HTD, treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Efficacy: Tumor response (ORR and DCR) will be evaluated according to RECIST Version 1.1; duration of response, PFS, and OS will also be evaluated.

Exploratory Immune Analysis: Immune responses will be detected and quantified in flow cytometry-based and serum assays.

Exploratory Molecular Profiling and Analysis: Genomic sequencing of tumor cells relative to non-tumor cells to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities; RNA sequencing to provide expression data and give relevance to DNA mutations; and quantitative proteomics to determine the exact amounts of specific proteins and to confirm expression of genes predictive of response and disease progression.
Statistical Methods: The rate of DLTs and the MTD or HTD will be assessed. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 within dose cohorts and for the overall study population in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. ORR and DCR will be evaluated according to RECIST Version 1.1 by dose cohort and overall; duration of response will also be evaluated. PFS and OS will be analyzed using Kaplan-Meier methods by dose cohort and overall.

Figure 1: Study Design and Treatment Schema

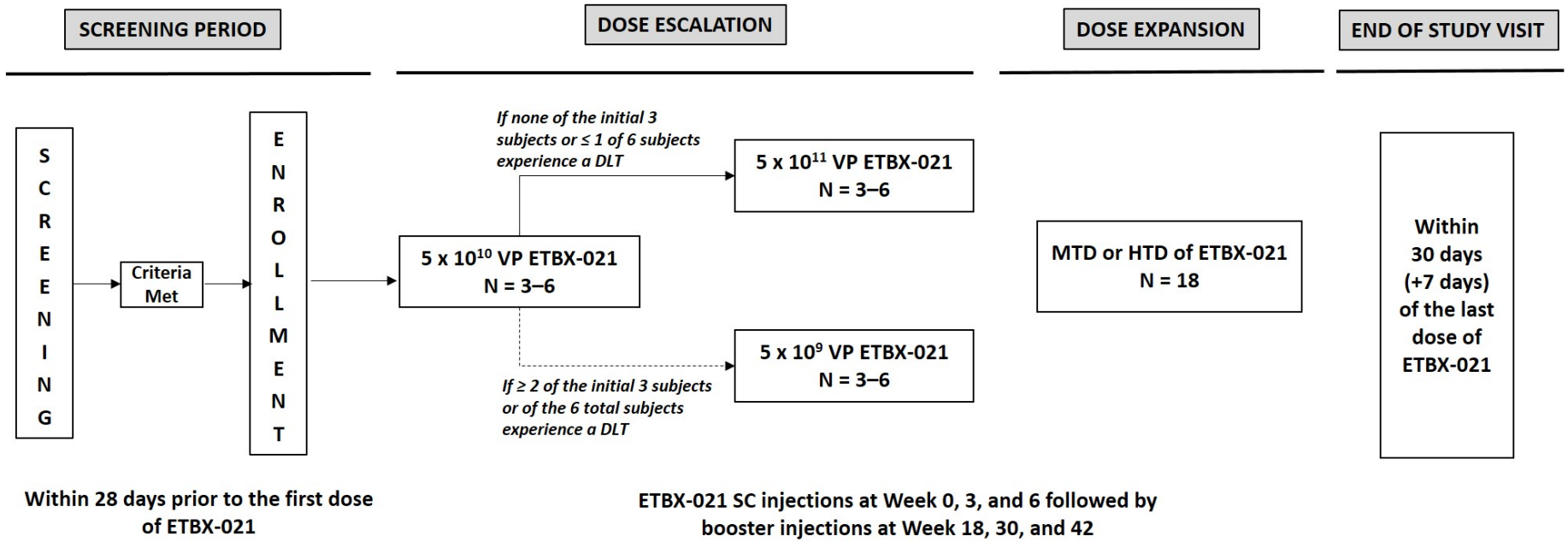


Table 3: Time and Events Schedule

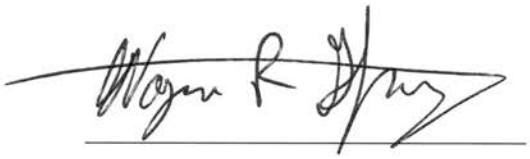
Assessment	Screening	Baseline	Treatment (Every 3-Week Dosing)				Boosters (Every 3-Month Dosing)						End of Study	Post Study Follow Up
Study Week	**Day -28 to -7**	**Day -7 to 1**	**0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Clinic Visit	X	X	X	X	X	X	X		X		X		X	
Informed Consent	X													
Inclusion/Exclusion	X	X												
Demographics	X													
Physical Examination, Height[a], Weight, ECOG	X	X	X	X	X	X	X		X		X		X	
Medical History[b]	X	X												
Confirm HER2 Expression	X													
Concomitant Medications	X	X	X	X	X	X	X		X		X		X	
Vital Signs[c]	X	X	X	X	X	X	X		X		X		X	
12-Lead ECG	X					X	X		X		X		X	
Echocardiogram/MUGA[d]	X					X	X		X		X		X	
Confirm Contraceptive Measures[e]	X													
Study Drug Injection/ Injection Site Reaction Monitoring[f]			X	X	X		X		X		X			
Dispensation of Subject Diary Card[g]			X	X	X		X		X		X			
Review of Subject Diary Card[g]				X	X	X		X		X		X		

Assessment	Screening	Baseline	Treatment (Every 3-Week Dosing)				Boosters (Every 3-Month Dosing)						End of Study	Post Study Follow Up
Study Week	**Day -28 to -7**	**Day -7 to 1**	**0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Telephone Contact 72 Hours Post Injection			X	X	X		X		X		X			
Tumor Imaging[h]		X				X		X		X		X	X	
Pregnancy Test[i]	X		X	X	X		X		X		X		X	
Urinalysis	X					X			X				X	
Chemistry Panel	X	X	X	X	X	X	X		X		X		X	
CBC, Differential, Platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X					X					X		X	
Serum Virology (HIV, HBV, HCV)	X													
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	
Exploratory Immune Analysis		X	X	X	X	X	X	X	X	X	X	X		
Exploratory Genomics and Proteomics Molecular Analysis		X												
Telephone Follow Up[j]														X

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase I Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-Expressing Breast Cancer
Study Number:	CMS-005
Final Date:	26 February 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:  Date: 2/26/16

Wayne R. Godfrey, MD
Chief Medical Officer
Medical and Safety Monitor
NantBioScience, Inc.

PROTOCOL NUMBER CMS-005

PHASE I STUDY OF AD5 [E1-, E2B-]-HER2/NEU VACCINE (ETBX-021) IN SUBJECTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC HER2-EXPRESSING BREAST CANCER

IND Number:	016,871
Principal Investigator:	Hatem Soliman, MD Moffitt Cancer Center 12902 Magnolia Drive Tampa, Florida 33612 Email: hatem.soliman@moffitt.org Office Phone: 813-745-4933
Clinical Study Sponsor:	NantBioScience, Inc.
Sponsor Contact: **(For medical questions/emergencies)**	Wayne R. Godfrey, MD Chief Medical Officer Medical and Safety Monitor Email: wayne@etubics.com Office Phone: 206-838-5110, Ext 9 Mobile Phone: 650-521-2770
Sponsor Contact: **(For study administration, operations, and execution questions)**	Jackie Imm, BA Clinical Trial Manager Email: Jackie.Imm@NantBio.com Office Phone: 919-694-6315
SAE Reporting:	Submit SAE Reports to one (1) of the following: SAE Email: SAE.Reporting@NantBio.com Fax: 800-853-3497

Protocol Version	Date
Original Protocol CMS-005	26 February 2016
Protocol CMS-005 Amendment 1	21 April 2016

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantBioScience, Inc.

Name of Investigational Product:
Ad5 [E1-, E2b-]-HER2/neu Vaccine, Suspension for Injection (ETBX-021)

Name of Active Ingredient:
Ad5 [E1-, E2b-]-HER2/neu

Title of Study:
Phase I Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-Expressing Breast Cancer

Study Number:
CMS-005

Study Phase:
Phase I

Primary Objectives:

- Determine the overall safety and recommended phase 2 dose of ETBX-021 when administered subcutaneously (SC) every 3 weeks for three injections followed by three booster injections at 3-month intervals to subjects with HER2-expressing breast cancer.

Secondary Objectives:

- Make preliminary assessments of objective response rate (ORR), disease control rate (DCR), duration of response, progression-free survival (PFS), and overall survival (OS) in subjects with HER2-expressing breast cancer treated with ETBX-021.

Exploratory Objectives:

- Evaluate the immunogenicity of ETBX-021 and determine the genomic and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

Primary Endpoints:

- Dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) or highest tested dose (HTD).
- Treatment-emergent adverse event (AEs) and serious adverse events (SAEs).
- Clinically significant changes in safety laboratory tests, physical examinations, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), and vital signs.

Secondary Endpoints:

- ORR (confirmed complete or partial response) according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- DCR (confirmed response or stable disease lasting for at least 6 months).
- Duration of response.
- PFS.

- OS.

Exploratory Endpoints:

- Immunogenicity of ETBX-021 by flow cytometric analysis of T-cell frequency, activation status, cytokine profiles, and antibody levels.
- Genetic and proteomic profiling and correlations with efficacy.

Study Design:

This is a Phase I trial in subjects with unresectable locally advanced or metastatic HER2-low expressing (IHC 1+ or 2+) breast cancer. The study will be conducted in two parts: the first part will involve dose escalation using a 3 + 3 design, and the second part will involve the expansion of the MTD or HTD to further evaluate safety, preliminary efficacy, and immunogenicity. In the first part, 3 to 6 subjects will be sequentially enrolled starting at dose cohort 1. Subjects will be assessed for dose-limiting toxicities (DLTs).

- Cohort 1: 5×10^{10} virus particles (VP).
- Cohort 2: 5×10^{11} VP.
- If needed, dose de-escalation cohort (cohort -1): 5×10^{9} VP.

Dose expansion will occur when the MTD or HTD has been determined. An additional 12 subjects will be enrolled in the dose expansion component of the trial, for a total of 18 subjects at the MTD or HTD.

Enrollment (planned):

Up to 30 subjects will be enrolled in the study. In the dose escalation component, 3 to 6 subjects will be sequentially enrolled starting at Cohort 1. In the dose expansion component (i.e., once the MTD or HTD has been identified), an additional 12 subjects will be enrolled for a total of 18 subjects in the MTD/HTD cohort to obtain further safety, preliminary efficacy, and immunogenicity data.

Diagnosis and Main Criteria for Inclusion:

Subjects must have histologically confirmed unresectable locally advanced or metastatic breast cancer that expresses HER2 (IHC 1+ or 2+). Subjects with HER2 IHC 3+ tumors are excluded.

Investigational Product, Dosage, and Mode of Administration:

ETBX-021 (5×10^{9}, 5×10^{10}, or 5×10^{11} VP in 1.0 mL) will be administered by SC injection every 3 weeks for 3 injections, followed by 3 booster injections at 3-month intervals.

Duration of Treatment:

Subjects will receive treatment for up to 42 weeks (injections at 0, 3, and 6 weeks with booster injections at 18, 30, and 42 weeks) or until they experience progressive disease or unacceptable toxicity, withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety: Safety endpoints include assessments of DLT, MTD or HTD, treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Efficacy: Tumor response (ORR and DCR) will be evaluated according to RECIST Version 1.1; duration of response, PFS, and OS will also be evaluated.

Exploratory Immune Analysis: Immune responses will be detected and quantified in flow cytometry-based and serum assays.

Exploratory Molecular Profiling and Analysis and its Rationale: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response to vaccine immunotherapy and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Statistical Methods:

The rate of DLTs and the MTD or HTD will be assessed. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 within dose cohorts and for the overall study population in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. ORR and DCR will be evaluated according to RECIST Version 1.1 by dose cohort and overall; duration of response will also be evaluated. PFS and OS will be analyzed using Kaplan-Meier methods by dose cohort and overall.

Figure 1: Study Design and Treatment Schema

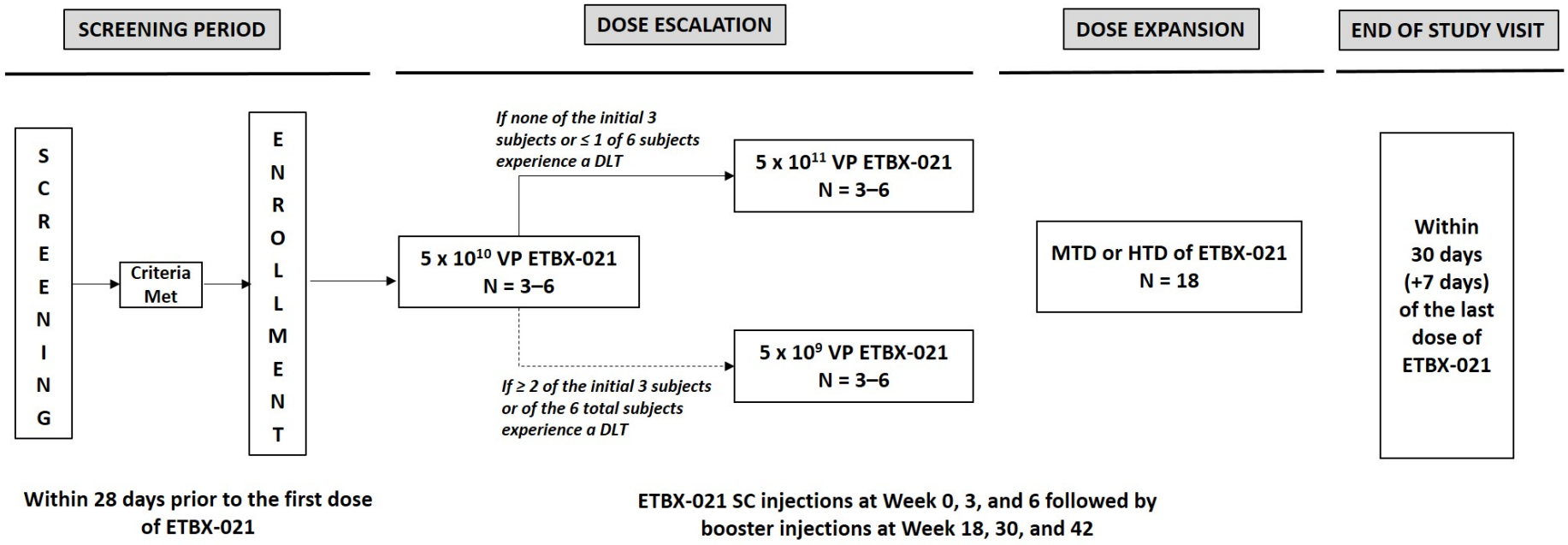


Table 3: Time and Events Schedule

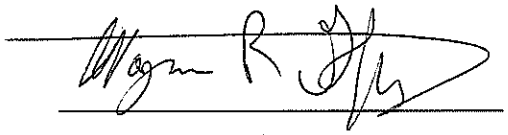
Assessment	**Screening**	**Treatment (Every 3-Week Dosing)**				**Boosters (Every 3-Month Dosing)**						**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/ 0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Clinic Visit	X	X	X	X	X	X	X	X	X	X	X	X	
Informed Consent	X												
Inclusion/Exclusion	X												
Demographics	X												
Physical Examination, Height[a], Weight, ECOG	X[b]	X[b]	X	X	X	X		X		X		X	
Medical History[c]	X	X											
Confirm HER2 Expression[d]	X												
Concomitant Medications	X	X	X	X	X	X		X		X		X	
Vital Signs[e]	X	X	X	X	X	X		X		X		X	
12-Lead ECG	X				X	X		X		X		X	
Echocardiogram/MUGA[f]	X				X	X		X		X		X	
Confirm Contraceptive Measures[g]	X												
Study Drug Injection/ Injection Site Reaction Monitoring[h]		X	X	X		X		X		X			
Dispensation of Subject Diary Card[i]		X	X	X		X		X		X			

Assessment	**Screening**	**Treatment (Every 3-Week Dosing)**				**Boosters (Every 3-Month Dosing)**						**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/ 0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Review of Subject Diary Card[i]			X	X	X		X		X		X	X	
Telephone Contact 72 Hours Post Injection		X	X	X		X		X		X			
Tumor Imaging[j]	X				X	X		X		X		X	
Pregnancy Test[k]	X[b]	X[b]	X	X		X		X		X		X	
Urinalysis	X				X			X				X	
Chemistry Panel	X[b]	X[b]	X	X	X	X		X		X		X	
CBC, Differential, Platelets	X[b]	X[b]	X	X	X	X		X		X		X	
Coagulation	X				X					X		X	
Serum Virology (HIV, HBV, HCV)[l]	X												
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	
Exploratory Immune Analysis		X	X	X	X	X	X	X	X	X	X		
Exploratory Genomics and Proteomics Molecular Analysis	X												
Telephone Follow Up[m]													X

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase I Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-Expressing Breast Cancer
Study Number:	CMS-005, Amendment 1
Final Date:	21 April 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:  Date: 4/21/16

Wayne R. Godfrey, MD
Chief Medical Officer
Medical and Safety Monitor
NantBioScience, Inc.

PROTOCOL NUMBER CMS-005

PHASE I STUDY OF AD5 [E1-, E2B-]-HER2/NEU VACCINE (ETBX-021) IN SUBJECTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC HER2-LOW-EXPRESSING (IHC 1+/2+) BREAST CANCER

IND Number:	016,871
Principal Investigator:	Hatem Soliman, MD Moffitt Cancer Center 12902 Magnolia Drive Tampa, Florida 33612 Email: hatem.soliman@moffitt.org Office Phone: 813-745-4933
Clinical Study Sponsor:	NantBioScience, Inc.
Sponsor Contact: **(For medical questions/emergencies)**	Wayne R. Godfrey, MD Chief Medical Officer Medical and Safety Monitor Email: wayne@etubics.com Office Phone: 206-838-5110, Ext 9 Mobile Phone: 650-521-2770
Sponsor Contact: **(For study administration, operations, and execution questions)**	Jackie Imm, BA Clinical Trial Manager Email: Jackie.Imm@NantBio.com Office Phone: 919-694-6315
SAE Reporting:	Submit SAE Reports to one (1) of the following: SAE Email: SAE.Reporting@NantBio.com Fax: 800-853-3497

Protocol Version	Date
Original Protocol CMS-005	26 February 2016
Protocol CMS-005 Amendment 1	20 April 2016
Protocol CMS-005 Amendment 2	25 May 2016

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantBioScience, Inc.

Name of Investigational Product:
Ad5 [E1-, E2b-]-HER2/neu Vaccine, Suspension for Injection (ETBX-021)

Name of Active Ingredient:
Ad5 [E1-, E2b-]-HER2/neu

Title of Study:
Phase I Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-Low-Expressing (IHC 1+/2+) Breast Cancer

Study Number:
CMS-005

Study Phase:
Phase I

Primary Objectives:

- Determine the overall safety and recommended phase 2 dose of ETBX-021 when administered subcutaneously (SC) every 3 weeks for three injections followed by three booster injections at 3-month intervals to subjects with HER2-low-expressing breast cancer.

Secondary Objectives:

- Make preliminary assessments of objective response rate (ORR), disease control rate (DCR), duration of response, progression-free survival (PFS), and overall survival (OS) in subjects with HER2-low-expressing breast cancer treated with ETBX-021.

Exploratory Objectives:

- Evaluate the immunogenicity of ETBX-021 and determine the genomic and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

Primary Endpoints:

- Dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) or highest tested dose (HTD).
- Treatment-emergent adverse event (AEs) and serious adverse events (SAEs).
- Clinically significant changes in safety laboratory tests, physical examinations, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), and vital signs.

Secondary Endpoints:

- ORR (confirmed complete or partial response) according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- DCR (confirmed response or stable disease lasting for at least 6 months).
- Duration of response.
- PFS.

- OS.

Exploratory Endpoints:

- Immunogenicity of ETBX-021 by flow cytometric analysis of T-cell frequency, activation status, cytokine profiles, and antibody levels.
- Genetic and proteomic profiling and correlations with efficacy.

Study Design:

This is a Phase I trial in subjects with unresectable locally advanced or metastatic HER2-low-expressing (IHC 1+ or 2+) breast cancer. The study will be conducted in two parts: the first part will involve dose escalation using a 3 + 3 design, and the second part will involve the expansion of the MTD or HTD to further evaluate safety, preliminary efficacy, and immunogenicity. In the first part, 3 to 6 subjects will be sequentially enrolled starting at dose cohort 1. Subjects will be assessed for dose-limiting toxicities (DLTs).

- Cohort 1: 5×10^{10} virus particles (VP).
- Cohort 2: 5×10^{11} VP.
- If needed, dose de-escalation cohort (cohort -1): 5×10^{9} VP.

Dose expansion will occur when the MTD or HTD has been determined. An additional 12 subjects will be enrolled in the dose expansion component of the trial, for a total of 18 subjects at the MTD or HTD.

Enrollment (planned):

Up to 30 subjects will be enrolled in the study. In the dose escalation component, 3 to 6 subjects will be sequentially enrolled starting at Cohort 1. In the dose expansion component (i.e., once the MTD or HTD has been identified), an additional 12 subjects will be enrolled for a total of 18 subjects in the MTD/HTD cohort to obtain further safety, preliminary efficacy, and immunogenicity data.

Diagnosis and Main Criteria for Inclusion:

Subjects must have histologically confirmed unresectable locally advanced or metastatic breast cancer that expresses HER2 (IHC 1+ or 2+). Subjects with HER2 IHC 3+ tumors are excluded.

Investigational Product, Dosage, and Mode of Administration:

ETBX-021 (5×10^{9}, 5×10^{10}, or 5×10^{11} VP in 1.0 mL) will be administered by SC injection every 3 weeks for 3 injections, followed by 3 booster injections at 3-month intervals.

Duration of Treatment:

Subjects will receive treatment for up to 42 weeks (injections at 0, 3, and 6 weeks with booster injections at 18, 30, and 42 weeks) or until they experience progressive disease or unacceptable toxicity, withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety: Safety endpoints include assessments of DLT, MTD or HTD, treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Efficacy: Tumor response (ORR and DCR) will be evaluated according to RECIST Version 1.1; duration of response, PFS, and OS will also be evaluated.

Exploratory Immune Analysis: Immune responses will be detected and quantified in flow cytometry-based and serum assays.

Exploratory Molecular Profiling and Analysis and its Rationale: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response to vaccine immunotherapy and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Statistical Methods:

The rate of DLTs and the MTD or HTD will be assessed. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 within dose cohorts and for the overall study population in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. ORR and DCR will be evaluated according to RECIST Version 1.1 by dose cohort and overall; duration of response will also be evaluated. PFS and OS will be analyzed using Kaplan-Meier methods by dose cohort and overall.

Figure 1: Study Design and Treatment Schema

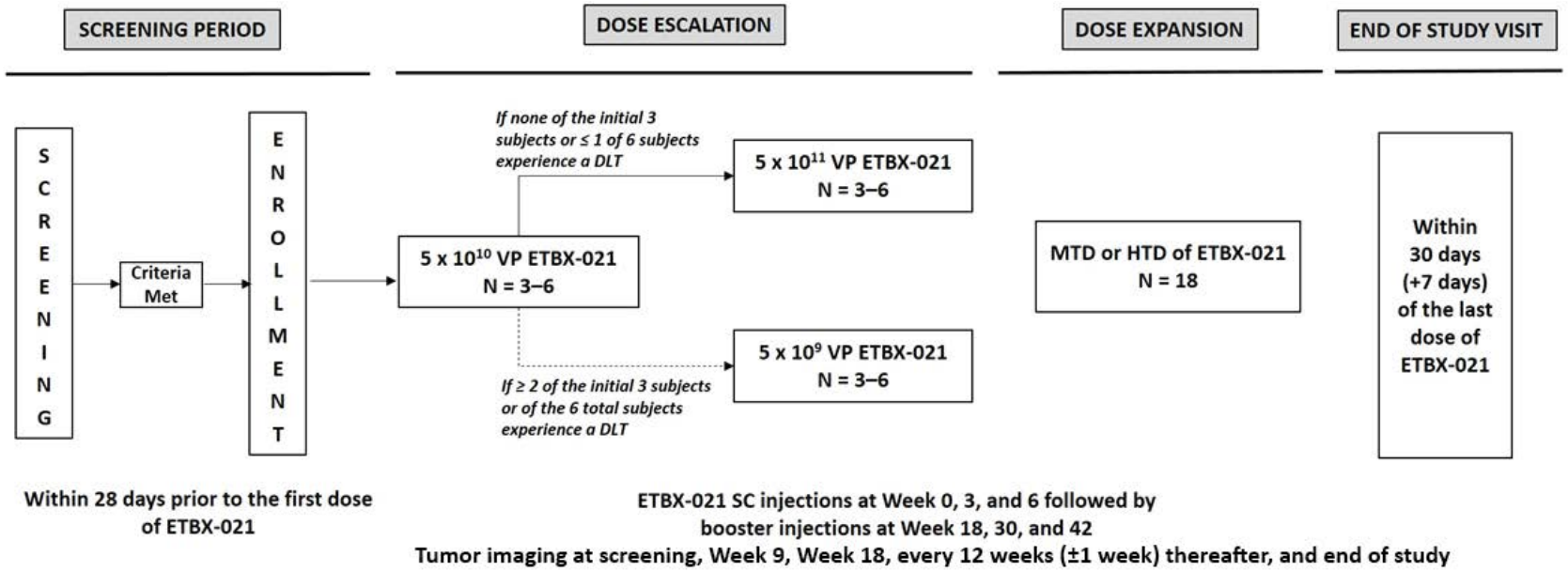


Table 3: Time and Events Schedule

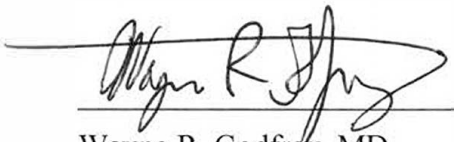
Assessment	**Screening**	**Treatment (Every 3-Week Dosing)**				**Boosters (Every 3-Month Dosing)**						**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/ 0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Clinic Visit	X	X	X	X	X	X	X	X	X	X	X	X	
Informed Consent	X												
Inclusion/Exclusion	X												
Demographics	X												
Physical Examination, Height[a], Weight, ECOG	X[b]	X[b]	X	X	X	X		X		X		X	
Medical History[c]	X	X											
Confirm HER2 Expression[d]	X												
Concomitant Medications	X	X	X	X	X	X		X		X		X	
Vital Signs[e]	X	X	X	X	X	X		X		X		X	
12-Lead ECG	X				X	X		X		X		X	
Echocardiogram/MUGA[f]	X				X	X		X		X		X	
Confirm Contraceptive Measures[g]	X												
Study Drug Injection/ Injection Site Reaction Monitoring[h]		X	X	X		X		X		X			
Dispensation of Subject Diary Card[i]		X	X	X		X		X		X			

Assessment	**Screening**	**Treatment (Every 3-Week Dosing)**				**Boosters (Every 3-Month Dosing)**						**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/ 0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Review of Subject Diary Card[i]			X	X	X		X		X		X	X	
Telephone Contact 72 Hours Post Injection		X	X	X		X		X		X			
Tumor Imaging[j]	X				X	X		X		X		X	
Pregnancy Test[k]	X[b]	X[b]	X	X		X		X		X		X	
Urinalysis	X				X			X				X	
Chemistry Panel	X[b]	X[b]	X	X	X	X		X		X		X	
CBC, Differential, Platelets	X[b]	X[b]	X	X	X	X		X		X		X	
Coagulation	X				X					X		X	
Serum Virology (HIV, HBV, HCV)[l]	X												
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	
Exploratory Immune Analysis		X	X	X	X	X	X	X	X	X	X		
Exploratory Genomics, Transcriptomics, and Proteomics Molecular Analysis	X												
Telephone Follow Up[m]													X

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase I Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-Low-Expressing (IHC 1+/2+) Breast Cancer
Study Number:	CMS-005, Amendment 2
Final Date:	25 May 2016

This clinical study protocol was subject to critical review and has been approved by the Sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed:  Date: 5/25/16

Wayne R. Godfrey, MD
Chief Medical Officer
Medical and Safety Monitor
NantBioScience, Inc.

PROTOCOL NUMBER QUILT-3.013 (CMS-005)

PHASE 1 STUDY OF AD5 [E1-, E2B-]-HER2/NEU VACCINE (ETBX-021) IN SUBJECTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC HER2-EXPRESSING (IHC 1+/2+/3+) CANCER

IND Number:	016,871
Clinical Study Sponsor:	NantBioScience, Inc.
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Senior Vice President Adult Medical Affairs, NantKwest Inc. 9920 Jefferson Blvd Culver City, CA 90232 Email: John.Lee@Nantkwest.com Cell Phone: +1-605-610-6391
Sponsor Contact: **(For study administration, operations, and execution questions)**	Jim Farmer Senior Director, Clinical Operations NantKwest, Inc Email: Jim.Farmer@Nantkwest.com Office Phone: 310-853-7522
SAE Reporting:	Submit SAE Reports to one of the following: SAE Email: SAE.Reporting@NantBio.com Fax: 800-853-3497

Protocol Version	Date
Original Protocol CMS-005	26 February 2016
Protocol CMS-005 Amendment 1	20 April 2016
Protocol CMS-005 Amendment 2	25 May 2016
Protocol QUILT-3.013 (CMS-005) Amendment 3	22 February 2018

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantBioScience, Inc.

Name of Investigational Product:
Ad5 [E1-, E2b-]-HER2/neu Vaccine, Suspension for Injection (ETBX-021)

Name of Active Ingredient:
Ad5 [E1-, E2b-]-HER2/neu

Title of Study:
Phase 1 Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-Expressing (IHC 1+/2+/3+) Cancer

Study Number:
QUILT-3.013 (formerly CMS-005)

Study Phase:
Phase 1

Primary Objectives:

- Determine the overall safety and recommended phase 2 dose of ETBX-021 when administered subcutaneously (SC) every 3 weeks for three injections followed by three booster injections at 3-month intervals to subjects with HER2-expressing cancer.

Secondary Objectives:

- Make preliminary assessments of objective response rate (ORR), disease control rate (DCR), duration of response, progression-free survival (PFS), and overall survival (OS) in subjects with HER2-expressing cancer treated with ETBX-021.

Exploratory Objectives:

- Evaluate the immunogenicity of ETBX-021 and determine the genomic and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

Primary Endpoints:

- Dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) or highest tested dose (HTD).
- Treatment-emergent adverse event (AEs) and serious adverse events (SAEs).
- Clinically significant changes in safety laboratory tests, physical examinations, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), and vital signs.

Secondary Endpoints:

- ORR (confirmed complete or partial response) according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- DCR (confirmed response or stable disease lasting for at least 6 months).
- Duration of response.
- PFS.
- OS.

Exploratory Endpoints:

- Immunogenicity of ETBX-021 by flow cytometric analysis of T-cell frequency, activation status, cytokine profiles, and antibody levels.
- Genetic and proteomic profiling and correlations with efficacy.

Study Design:

This is a phase 1 trial in subjects with unresectable locally advanced or metastatic HER2-expressing (IHC 1+, 2+, or 3+) cancer. The study will be conducted in two parts: the first part will involve dose escalation using a 3 + 3 design, and the second part will involve the expansion of the MTD or HTD to further evaluate safety, preliminary efficacy, and immunogenicity. In the first part, 3 to 6 subjects will be sequentially enrolled starting at dose cohort 1. Subjects will be assessed for dose-limiting toxicities (DLTs).

- Cohort 1: 5×10^{10} virus particles (VP).
- Cohort 2: 5×10^{11} VP.
- If needed, dose de-escalation cohort (cohort -1): 5×10^{9} VP.

Dose expansion will occur when the MTD or HTD has been determined. An additional 12 subjects will be enrolled in the dose expansion component of the trial, for a total of 18 subjects at the MTD or HTD.

Enrollment (planned):

Up to 30 subjects will be enrolled in the study. In the dose escalation component, 3 to 6 subjects will be sequentially enrolled starting at cohort 1. In the dose expansion component (ie, once the MTD or HTD has been identified), an additional 12 subjects will be enrolled for a total of 18 subjects in the MTD/HTD cohort to obtain further safety, preliminary efficacy, and immunogenicity data.

Diagnosis and Main Criteria for Inclusion:

Subjects must have histologically confirmed unresectable locally advanced or metastatic cancer that expresses HER2 (IHC 1+, 2+, or 3+).

Investigational Product, Dosage, and Mode of Administration:

ETBX-021 (5×10^{9}, 5×10^{10}, or 5×10^{11} VP in 1.0 mL) will be administered by SC injection every 3 weeks for 3 injections, followed by 3 booster injections at 3-month intervals.

Duration of Treatment:

Subjects will receive treatment for up to 42 weeks (injections at 0, 3, and 6 weeks with booster injections at 18, 30, and 42 weeks) or until they experience progressive disease or unacceptable toxicity, withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety: Safety endpoints include assessments of DLT, MTD or HTD, treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Efficacy: Tumor response (ORR and DCR) will be evaluated according to RECIST Version 1.1; duration of response, PFS, and OS will also be evaluated.

Exploratory Immune Analysis: Immune responses will be detected and quantified in flow cytometry-based and serum assays.

Exploratory Molecular Profiling, Analysis, and Rationale: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response to vaccine immunotherapy and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Statistical Methods:

The rate of DLTs and the MTD or HTD will be assessed. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 within dose cohorts and for the overall study population in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. ORR and DCR will be evaluated according to RECIST Version 1.1 by dose cohort and overall; duration of response will also be evaluated. PFS and OS will be analyzed using Kaplan-Meier methods by dose cohort and overall.

Figure 1: Study Design and Treatment Schema

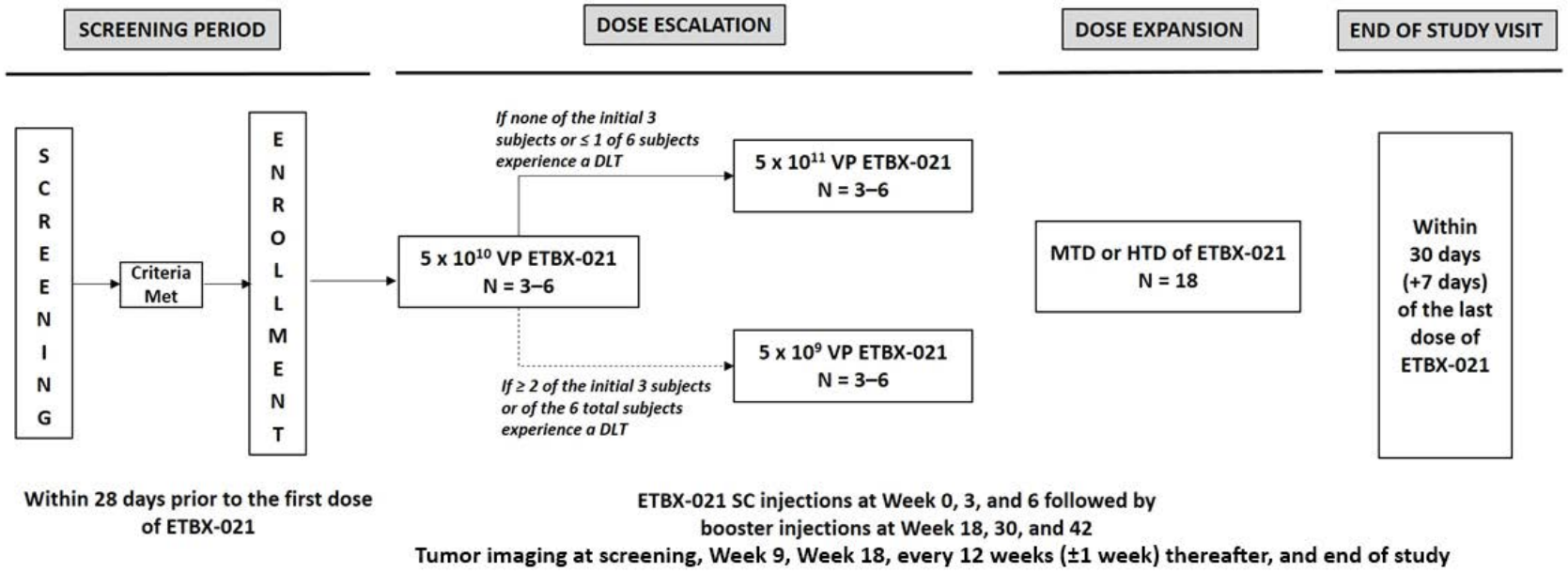


Table 3: Time and Events Schedule

Assessment	**Screening**	**Treatment (Every 3-Week Dosing)**				**Boosters (Every 3-Month Dosing)**						**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/ 0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Clinic Visit	X	X	X	X	X	X	X	X	X	X	X	X	
Informed Consent	X												
Inclusion/Exclusion	X												
Demographics	X												
Physical Examination, Height[a], Weight, ECOG	X[b]	X[b]	X	X	X	X		X		X		X	
Medical History[c]	X	X											
Confirm HER2 Expression[d]	X												
Concomitant Medications	X	X	X	X	X	X		X		X		X	
Vital Signs[e]	X	X	X	X	X	X		X		X		X	
12-Lead ECG	X				X	X		X		X		X	
Echocardiogram/MUGA[f]	X				X	X		X		X		X	
Confirm Contraceptive Measures[g]	X												
Study Drug Injection/ Injection Site Reaction Monitoring[h]		X	X	X		X		X		X			
Dispensation of Subject Diary Card[i]		X	X	X		X		X		X			

Assessment	**Screening**	**Treatment (Every 3-Week Dosing)**				**Boosters (Every 3-Month Dosing)**						**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/ 0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Review of Subject Diary Card[i]			X	X	X		X		X		X	X	
Telephone Contact 72 Hours Post Injection		X	X	X		X		X		X			
Tumor Imaging[j]	X				X	X		X		X		X	
Pregnancy Test[k]	X[b]	X[b]	X	X		X		X		X		X	
Urinalysis	X				X			X				X	
Chemistry Panel	X[b]	X[b]	X	X	X	X		X		X		X	
CBC, Differential, Platelets	X[b]	X[b]	X	X	X	X		X		X		X	
Coagulation	X				X					X		X	
Serum Virology (HIV, HBV, HCV)[l]	X												
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	
Exploratory Immune Analysis		X	X	X	X	X	X	X	X	X	X		
Exploratory Genomics, Transcriptomics, and Proteomics Molecular Analysis	X												
Telephone Follow Up[m]													X

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase 1 Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-expressing (IHC 1+/2+/3+) Cancer
Study Number:	QUILT-3.013 (CMS-005), Amendment 3
Final Date:	22 February 2018

This clinical study protocol was subject to critical review and has been approved by NantBioScience, Inc. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: Feb 22 2018

John H. Lee, MD
Senior Vice President Adult Medical Affairs,
NantKwest Inc.
9920 Jefferson Blvd
Culver City, CA 90232
Email: John.Lee@Nantkwest.com
Cell Phone: +1-605-610-6391

PROTOCOL NUMBER QUILT-3.013 (CMS-005)

PHASE 1 STUDY OF AD5 [E1-, E2B-]-HER2/NEU VACCINE (ETBX-021) IN SUBJECTS WITH UNRESECTABLE LOCALLY ADVANCED OR METASTATIC HER2-EXPRESSING (IHC 1+/2+/3+) CANCER

IND Number:	016,871
Clinical Study Sponsor:	NantBio, Inc.
Sponsor Contact: **(For medical questions/emergencies)**	John H. Lee, MD Senior Vice President Adult Medical Affairs, NantKwest Inc. 9920 Jefferson Blvd Culver City, CA 90232 Email: John.Lee@Nantkwest.com Cell Phone: +1-605-610-6391
Sponsor Contact: **(For study administration, operations, and execution questions)**	Jim Farmer Senior Director, Clinical Operations NantKwest, Inc Email: Jim.Farmer@Nantkwest.com Office Phone: 310-853-7522
SAE Reporting:	Submit SAE Reports to one of the following: SAE Email: SAE.Reporting@NantBio.com Fax: 800-853-3497

Protocol Version	Date
Original Protocol CMS-005	26 February 2016
Protocol CMS-005 Amendment 1	20 April 2016
Protocol CMS-005 Amendment 2	25 May 2016
Protocol QUILT-3.013 (CMS-005) Amendment 3	22 February 2018
Protocol QUILT-3.013 (CMS-005) Amendment 4	1 May 2018

PROTOCOL SYNOPSIS

Name of Sponsor/Company:
NantBio, Inc.

Name of Investigational Product:
Ad5 [E1-, E2b-]-HER2/neu Vaccine, Suspension for Injection (ETBX-021)

Name of Active Ingredient:
Ad5 [E1-, E2b-]-HER2/neu

Title of Study:
Phase 1 Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-Expressing (IHC 1+/2+/3+) Cancer

Study Number:
QUILT-3.013 (formerly CMS-005)

Study Phase:
Phase 1

Primary Objectives:

- Determine the overall safety and recommended phase 2 dose of ETBX-021 when administered subcutaneously (SC) every 3 weeks for three injections followed by three booster injections at 3-month intervals to subjects with HER2-expressing cancer.

Secondary Objectives:

- Make preliminary assessments of objective response rate (ORR), disease control rate (DCR), duration of response, progression-free survival (PFS), and overall survival (OS) in subjects with HER2-expressing cancer treated with ETBX-021.

Exploratory Objectives:

- Evaluate the immunogenicity of ETBX-021 and determine the genomic and proteomic profile of subjects' tumors to identify gene mutations, gene amplifications, RNA-expression levels, and protein-expression levels. Correlations between genomic/proteomic profiles and efficacy outcomes will be assessed.

Primary Endpoints:

- Dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) or highest tested dose (HTD).
- Treatment-emergent adverse event (AEs) and serious adverse events (SAEs).
- Clinically significant changes in safety laboratory tests, physical examinations, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF), and vital signs.

Secondary Endpoints:

- ORR (confirmed complete or partial response) according to the Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1.
- DCR (confirmed response or stable disease lasting for at least 6 months).
- Duration of response.
- PFS.
- OS.

Exploratory Endpoints:

- Immunogenicity of ETBX-021 by flow cytometric analysis of T-cell frequency, activation status, cytokine profiles, and antibody levels.
- Genetic and proteomic profiling and correlations with efficacy.

Study Design:

This is a phase 1 trial in subjects with unresectable locally advanced or metastatic HER2-expressing (IHC 1+, 2+, or 3+) cancer. The study will be conducted in two parts: the first part will involve dose escalation using a 3 + 3 design, and the second part will involve the expansion of the MTD or HTD to further evaluate safety, preliminary efficacy, and immunogenicity. In the first part, 3 to 6 subjects will be sequentially enrolled starting at dose cohort 1. Subjects will be assessed for dose-limiting toxicities (DLTs).

- Cohort 1: 5×10^{10} virus particles (VP).
- Cohort 2: 5×10^{11} VP.
- If needed, dose de-escalation cohort (cohort -1): 5×10^{9} VP.

Dose expansion will occur when the MTD or HTD has been determined. An additional 12 subjects will be enrolled in the dose expansion component of the trial, for a total of 18 subjects at the MTD or HTD.

Enrollment (planned):

Up to 30 subjects will be enrolled in the study. In the dose escalation component, 3 to 6 subjects will be sequentially enrolled starting at cohort 1. In the dose expansion component (ie, once the MTD or HTD has been identified), an additional 12 subjects will be enrolled for a total of 18 subjects in the MTD/HTD cohort to obtain further safety, preliminary efficacy, and immunogenicity data.

Diagnosis and Main Criteria for Inclusion:

Subjects must have histologically confirmed unresectable locally advanced or metastatic cancer that expresses HER2 (IHC 1+, 2+, or 3+). For malignancies other than breast and gastrointestinal, HER2 expression must be confirmed by a validated in situ hybridization (ISH) assay with results considered positive of HER2 amplification by ASCO/CAP HER2 testing guideline.

Investigational Product, Dosage, and Mode of Administration:

ETBX-021 (5×10^{9}, 5×10^{10}, or 5×10^{11} VP in 1.0 mL) will be administered by SC injection every 3 weeks for 3 injections, followed by 3 booster injections at 3-month intervals.

Duration of Treatment:

Subjects will receive treatment for up to 42 weeks (injections at 0, 3, and 6 weeks with booster injections at 18, 30, and 42 weeks) or until they experience progressive disease or unacceptable toxicity, withdraw consent, or if the Investigator feels it is no longer in their best interest to continue treatment.

Reference Therapy, Dosage, and Mode of Administration:

Not applicable.

Criteria for Evaluation:

Safety: Safety endpoints include assessments of DLT, MTD or HTD, treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. Toxicities will be graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

Efficacy: Tumor response (ORR and DCR) will be evaluated according to RECIST Version 1.1; duration of response, PFS, and OS will also be evaluated.

Exploratory Immune Analysis: Immune responses will be detected and quantified in flow cytometry-based and serum assays.

Exploratory Molecular Profiling, Analysis, and Rationale: Genomic sequencing of tumor cells from tissue relative to non-tumor cells from whole blood will be profiled to identify the genomic variances that may contribute to response or disease progression and provide an understanding of molecular abnormalities. RNA sequencing will be conducted to provide expression data and give relevance to DNA mutations. Quantitative proteomics analysis will be conducted to determine the exact amounts of specific proteins and to confirm expression of genes that are correlative of response to vaccine immunotherapy and disease progression. All genomic, transcriptomic, and proteomic molecular analyses will be retrospective and exploratory.

Statistical Methods:

The rate of DLTs and the MTD or HTD will be assessed. Overall safety will be assessed by descriptive analyses using tabulated frequencies of AEs by grade using CTCAE Version 4.03 within dose cohorts and for the overall study population in terms of treatment-emergent AEs, SAEs, and clinically significant changes in safety laboratory tests, physical examinations, ECGs, LVEF, and vital signs. ORR and DCR will be evaluated according to RECIST Version 1.1 by dose cohort and overall; duration of response will also be evaluated. PFS and OS will be analyzed using Kaplan-Meier methods by dose cohort and overall.

Figure 1: Study Design and Treatment Schema

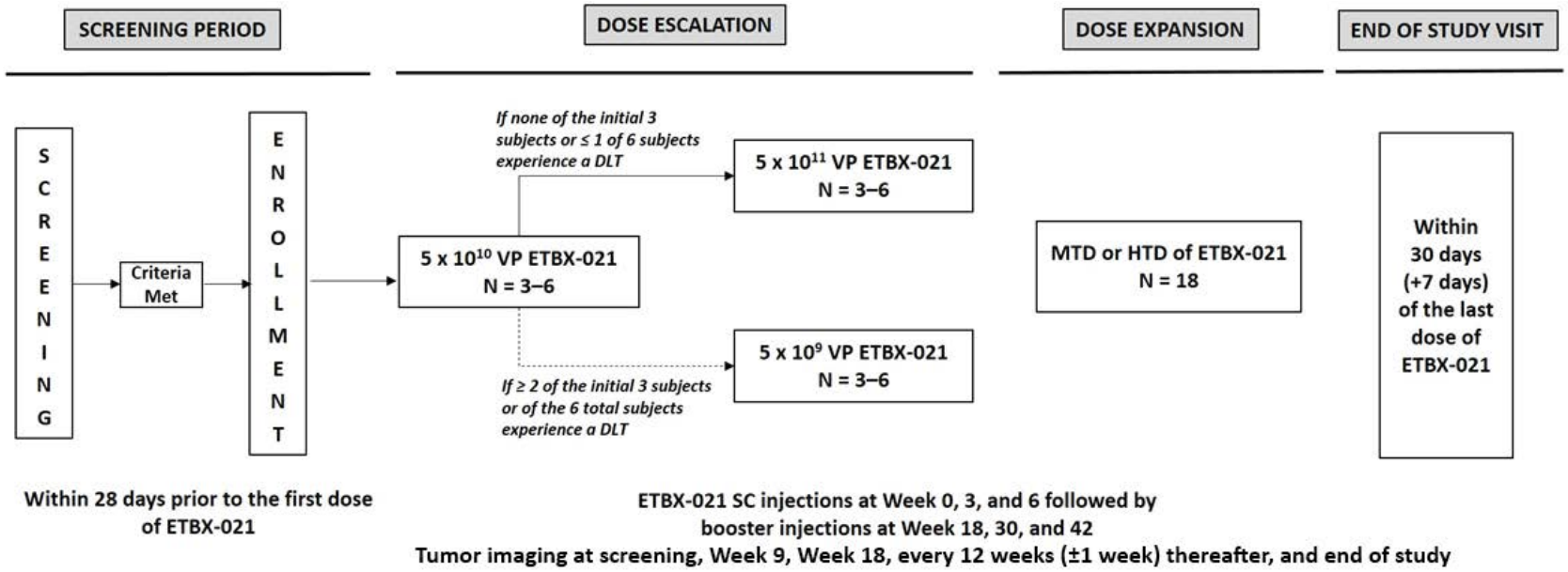


Table 3: Time and Events Schedule

Assessment	**Screening**	**Treatment (Every 3-Week Dosing)**				**Boosters (Every 3-Month Dosing)**						**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/ 0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Clinic Visit	X	X	X	X	X	X	X	X	X	X	X	X	
Informed Consent	X												
Inclusion/Exclusion	X												
Demographics	X												
Physical Examination, Height[a], Weight, ECOG	X[b]	X[b]	X	X	X	X		X		X		X	
Medical History[c]	X	X											
Confirm HER2 Expression[d]	X												
Concomitant Medications	X	X	X	X	X	X		X		X		X	
Vital Signs[e]	X	X	X	X	X	X		X		X		X	
12-Lead ECG	X				X	X		X		X		X	
Echocardiogram/MUGA[f]	X				X	X		X		X		X	
Confirm Contraceptive Measures[g]	X												
Study Drug Injection/ Injection Site Reaction Monitoring[h]		X	X	X		X		X		X			
Dispensation of Subject Diary Card[i]		X	X	X		X		X		X			

Assessment	**Screening**	**Treatment (Every 3-Week Dosing)**				**Boosters (Every 3-Month Dosing)**						**End of Study**	**Post Study Follow Up**
Study Week	**Day -28 to -1**	**Baseline/ 0**	**3**	**6**	**9**	**18**	**21**	**30**	**33**	**42**	**45**		
Review of Subject Diary Card[i]			X	X	X		X		X		X	X	
Telephone Contact 72 Hours Post Injection		X	X	X		X		X		X			
Tumor Imaging[j]	X				X	X		X		X		X	
Pregnancy Test[k]	X[b]	X[b]	X	X		X		X		X		X	
Urinalysis	X				X			X				X	
Chemistry Panel	X[b]	X[b]	X	X	X	X		X		X		X	
CBC, Differential, Platelets	X[b]	X[b]	X	X	X	X		X		X		X	
Coagulation	X				X					X		X	
Serum Virology (HIV, HBV, HCV)[l]	X												
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	
Exploratory Immune Analysis		X	X	X	X	X	X	X	X	X	X		
Exploratory Genomics, Transcriptomics, and Proteomics Molecular Analysis	X												
Telephone Follow Up[m]													X

APPENDIX 2. SPONSOR SIGNATURE

Study Title:	Phase 1 Study of Ad5 [E1-, E2b-]-HER2/neu Vaccine (ETBX-021) in Subjects with Unresectable Locally Advanced or Metastatic HER2-expressing (IHC 1+/2+/3+) Cancer
Study Number:	QUILT-3.013 (CMS-005), Amendment 4
Final Date:	1 May 2018

This clinical study protocol was subject to critical review and has been approved by NantBio, Inc. The following personnel contributed to writing and/or approving this protocol:

Signed: _____ Date: 5-2-18

John H. Lee, MD
Senior Vice President Adult Medical Affairs,
NantKwest Inc.
9920 Jefferson Blvd
Culver City, CA 90232
Email: John.Lee@Nantkwest.com
Cell Phone: +1-605-610-6391