CytRx® CORPORATION

CLINICAL PROTOCOL

TITLE:	**A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma**
PROTOCOL NUMBER:	**INNO-206-P2-STS-01**
STUDY DRUG:	**INNO-206**
IND NUMBER:	**113,695**
EUDRACT NUMBER:	**2011-004927-11**
SPONSOR:	**CytRx Corporation 11726 San Vicente Blvd Los Angeles, CA 90049 (310) 826-5648 FAX: (310) 826-6139**
SAFETY HOTLINE:	**Toll-free: 1-877-462-0134**
SAFETY FAX:	**Toll-free: 1-877-464-7787**
DATE OF PROTOCOL:	**November 14, 2011**

PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by CytRx Corporation prior to seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The study will be conducted in accordance with current United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: Daniel Levitt MD

Daniel Levitt, M.D., Ph.D.
Chief Medical Officer
CytRx Corporation

Date: Nov. 18, 2011

1. SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma	
Primary Objectives: The primary objective of this study is to determine the preliminary efficacy of administration of INNO-206 compared to doxorubicin in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by progression-free survival, progression-free survival at 3 and 6 months, tumor response and overall survival. **Secondary Objectives:** The secondary objective of this study is to evaluate the safety of INNO-206 compared to doxorubicin in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, multiple-gated acquisition (MUGA) scans/cardiac ultrasound evaluations, electrocardiogram (ECG) results, and weight.	
Study Rationale and Significance: INNO-206 is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months. Three-year survival rates as high as 30% have been observed in some clinical studies. Several chemotherapy regimens have been explored as palliative therapy for subjects with advanced soft tissue sarcomas. Combinations of ifosfamide and doxorubicin appear to offer the highest response rates and longest time to progression. However, these regimens are quite toxic and have not significantly increased survival in these individuals. INNO-206 may improve the activity of doxorubicin without increasing its toxicity as has been demonstrated in animal studies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b

Study Design and Methodology:

This is a phase 2b open-label study evaluating the preliminary efficacy and safety of INNO-206 administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously (IV) on Day 1 every 21 days for up to 6 consecutive cycles compared to doxorubicin administered at 75 mg/m^2 for up to 6 consecutive cycles. Subjects will be randomized 2:1 to receive either INNO-206 or doxorubicin.

Tumor response will be monitored prior to (within 5 days) of Cycles 3 and 6 (then every 2 months for 8 months, then every 3 months until disease progression) using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and treatment will continue every 21 days until tumor progression is observed, 6 cycles of treatment are completed or unacceptable toxicity occurs. Progression-free survival [PFS], progression-free survival at 3 and 6 months and overall survival [OS] will be monitored as other primary objectives. Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, ECOG and ECGs will be performed. Cardiac function will also be followed periodically using either MUGA scans or cardiac ultrasounds.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Subjects must meet the following criteria to be included in the study:

1. Age between 15 and 80 years (US only), and 18-80 (rest of world (ROW)), male or female.
2. Adjuvant or neoadjuvant chemotherapy (including doxorubicin) allowed if no tumor recurrence for at least 12 months since the last measurement, beginning or end of last chemotherapy.
3. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma of intermediate or high grade.
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG performance status 0-2.
6. Life expectancy >12 weeks.
7. Measurable tumor lesions according to RECIST 1.1 criteria.
8. Women must not be able to become pregnant (eg post menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
9. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
10. Geographic accessibility to the site that ensures the subject will be able to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior chemotherapy unless for adjuvant or neoadjuvant therapy with no tumor recurrence for at least 12 months.
2. Prior exposure to >3 cycles or 225 mg/m^2 of doxorubicin or Doxil®.
3. Palliative surgery and/or radiation treatment less than 4 weeks prior to Randomization.
4. Exposure to any investigational agent within 30 days of Randomization.
5. Current Stage 1 or 2 soft tissue sarcomas.
6. Current evidence/diagnosis of alveolar soft part sarcoma, chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma, Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, radiation-induced sarcomas and unresectable low grade liposarcomas.
7. Evidence of central nervous system (CNS) metastasis (negative imaging study within 4 weeks of Screening Visit or during Screening).
8. History of other malignancies except cured basal cell carcinoma, superficial bladder cancer or carcinoma in situ of the cervix unless documented free of cancer for ≥5 years.
9. Laboratory values: Screening serum creatinine >1.5x upper limit of normal (ULN), alanine aminotransferase (ALT) > 3 × ULN or >5 × ULN if liver metastases are present, total bilirubin >3 × ULN, absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <25% for females or <27% for males, or coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN, albumin <2.0 g/dL.
10. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b

11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.
12. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed
13. History or signs of active coronary artery disease with or without angina pectoris.
14. Serious myocardial dysfunction defined as scintigraphically (eg MUGA, myocardial scintigram) or ultrasound determined absolute left ventricular ejection fraction (LVEF) <45% of predicted.
15. History of HIV infection.
16. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
17. Major surgery within 3 weeks prior to Randomization.
18. Substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
19. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
One hundred and five (105) study subjects will be randomized 2:1 (INNO-206:doxorubicin) at approximately 30 study centers in the United States (US), Hungary, Romania, Ukraine, Russia, India, and Australia. Up to 32 subjects may be enrolled in India, with the remaining subjects distributed in the other locations.

Test Product, Dose and Mode of Administration:
Lyophilized powder in vials that contain 200 mg of INNO-206 reconstituted by adding a sterile solution of 50% ethanol: 50% water, administration completed within 2 hours (of being reconstituted) as a 30 minute IV infusion in Lactated Ringer's solution. Total dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent).

Reference Therapy, Dose and Mode of Administration:
Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. Prepare IV infusion per the package insert (see the Study Reference Manual).

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:

- Progression-free survival
- Overall survival
- Objective tumor response (RECIST 1.1 criteria)
- 3 and 6 month progression-free survival

Safety:
The following safety variables will be assessed over 16 weeks:

- Adverse events
- Ability to remain on assigned treatment (tolerability)
- Clinical and laboratory data including physical examinations, vital signs, weight, MUGA/cardiac ultrasound evaluations, ECG results and laboratory test results
- Use of concomitant medications

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b

Statistical Methods:

In accordance with the intention-to-treat principle, all randomized subjects who enter active treatment and have had at least 1 dose of study medication and 1 post-dose efficacy measurement will be included in the primary statistical analyses according to the treatment group to which they were originally assigned.

Efficacy:

Tumor response will be monitored prior to Cycle 3 and 6 as well as every 2 months for 8 months from randomization, then every 3 months until disease progression. For the estimation of progression-free and overall survival a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at 3 and 6 months.

Safety:

The safety data will be summarized by treatment group. The treatment groups will be compared with respect to occurrence of each AE. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be compared between groups using Fisher's exact test. Adverse events, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimens. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	End of Treatment[17]	Every 2 or 3 mo.[16]	Follow Up[14]
Signed informed consent	X									
Review inclusion/exclusion	X	X								
Medical history[1]	X									
Physical examination	X	X	X	X	X	X	X	X[18]	X	
Height (cm)	X									
Weight (kg)	X	X	X	X	X	X	X			
BSA calculation[2]		X	X	X	X	X	X			
Vital signs[3]	X	X	X	X	X	X	X	X		
ECOG PS	X	X	X	X	X	X	X	X		
CT/ MRI scan / tumor measurements[4]	X[9]			X[8]			X[8]	X[12]	X[8]	
Chest x-ray	X[10]							X[10,12]		
Bone scan or PET/CT	X[15]									
ECG	X	X	X	X	X	X	X	X[12]	X	
ECHO (with ejection fraction) or MUGA/cardiac ultrasound	X		X		X		X	X	X	
CBC w/differential & plts[5]	X	X[20]	X	X	X	X	X	X[13]	X	
Serum chemistries[5,6]	X	X[20]	X	X	X	X	X	X[13]		
Urinalysis[7]	X							X[13]		
Serum troponin	X	X[20]	X	X	X	X	X	X[13]	X	
Serum/urine pregnancy test	X									
Randomization		X[19]								
INNO-206 or doxorubicin admin administration[21]		X	X	X	X	X	X			
Blood alcohol level[22]										
Concomitant medications	X[11]	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X		
Telephone call										X

NOTE: All assessments must be performed within 72 hr of each specified time parameter, except Cycle 1 (see Section 7 for details).

CLINICAL PROTOCOL

TITLE:	**A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma**
PROTOCOL NUMBER:	**INNO-206-P2-STS-01**
STUDY DRUG:	**INNO-206**
IND NUMBER:	**113,695**
EUDRACT NUMBER:	**2011-004927-11**
SPONSOR:	**CytRx Corporation** **11726 San Vicente Blvd** **Los Angeles, CA 90049** **(310) 826-5648** **FAX: (310) 826-6139**
SAFETY HOTLINE:	**Toll-free: 1-877-462-0134**
SAFETY FAX:	**Toll-free: 1-877-464-7787**
DATE OF PROTOCOL:	**November 14, 2011**
AMENDMENT 1:	**December 16, 2011**

PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma

By signing below, the Investigator agrees to adhere to the protocol as outlined and agrees that any changes to the protocol must be approved by CytRx Corporation prior to seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The study will be conducted in accordance with current United States (US) Food and Drug Administration (FDA) regulations, International Conference on Harmonization (ICH) guidelines, Good Clinical Practice (GCP) guidelines, the principles of the Declaration of Helsinki, and other applicable regulations and guidelines.

Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: Daniel Levitt MD

Daniel Levitt, M.D., Ph.D.
Chief Medical Officer
CytRx Corporation

Date: December 16, 2011

1. SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma	
Primary Objectives: The primary objective of this study is to determine the preliminary efficacy of administration of INNO-206 compared to doxorubicin in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by progression-free survival, progression-free survival at 4 and 6 months, tumor response and overall survival. **Secondary Objectives:** The secondary objective of this study is to evaluate the safety of INNO-206 compared to doxorubicin in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, multiple-gated acquisition (MUGA) scans/cardiac ultrasound evaluations, electrocardiogram (ECG) results, and weight.	
Study Rationale and Significance: INNO-206 is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months. Three-year survival rates as high as 30% have been observed in some clinical studies. Several chemotherapy regimens have been explored as palliative therapy for subjects with advanced soft tissue sarcomas. Combinations of ifosfamide and doxorubicin appear to offer the highest response rates and longest time to progression. However, these regimens are quite toxic and have not significantly increased survival in these individuals. INNO-206 may improve the activity of doxorubicin without increasing its toxicity as has been demonstrated in animal studies.	

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b

Study Design and Methodology:

This is a phase 2b open-label study evaluating the preliminary efficacy and safety of INNO-206 administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously (IV) on Day 1 every 21 days for up to 6 consecutive cycles compared to doxorubicin administered at 75 mg/m^2 for up to 6 consecutive cycles. Subjects will be randomized 2:1 to receive either INNO-206 or doxorubicin.

Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, ECOG and ECGs will be performed. Cardiac function will also be followed periodically using either MUGA scans or cardiac ultrasounds. Treatment will continue every 21 days until tumor progression is observed, 6 cycles of treatment are completed or unacceptable toxicity occurs.

Tumor response will be monitored every 60 days (2 months) after Cycle 1-Day 1 until Day 240 (8 months), then every 3 months until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria, and. Progression-free survival [PFS], progression-free survival at 4 and 6 months and overall survival [OS] will be monitored as other primary objectives.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b

Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Subjects must meet the following criteria to be included in the study:

1. Age between 15-80 years (US only), and 18-80 (rest of world (ROW)), male or female.
2. Adjuvant or neoadjuvant chemotherapy (including doxorubicin) allowed if no tumor recurrence for at least 12 months since the last measurement, beginning or end of last chemotherapy.
3. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma of intermediate or high grade.
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG performance status 0-2.
6. Life expectancy >12 weeks.
7. Measurable tumor lesions according to RECIST 1.1 criteria.
8. Women must not be able to become pregnant (eg post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
9. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
10. Geographic accessibility to the site that ensures the subject will be able to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior chemotherapy unless for adjuvant or neoadjuvant therapy with no tumor recurrence for at least 12 months.
2. Prior exposure to >3 cycles or 225 mg/m^2 of doxorubicin or Doxil®.
3. Palliative surgery and/or radiation treatment less than 4 weeks prior to Randomization.
4. Exposure to any investigational agent within 30 days of Randomization.
5. Current Stage 1 or 2 soft tissue sarcomas.
6. Current evidence/diagnosis of alveolar soft part sarcoma, chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma, Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas and unresectable low grade liposarcomas.
7. Central nervous system metastasis
8. History of other malignancies except cured basal cell carcinoma, superficial bladder cancer or carcinoma in situ of the cervix unless documented free of cancer for $\geq$5 years.
9. Laboratory values: Screening serum creatinine >1.5x upper limit of normal (ULN), alanine aminotransferase (ALT) > 3 × ULN or >5 × ULN if liver metastases are present, total bilirubin >3 × ULN, absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <25% for females or <27% for males, or coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN, albumin <2.0 g/dL.
10. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b

11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.
12. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed
13. History or signs of active coronary artery disease with or without angina pectoris.
14. Serious myocardial dysfunction defined as scintigraphically (eg MUGA, myocardial scintigram) or ultrasound determined absolute left ventricular ejection fraction (LVEF) <45% of predicted.
15. History of HIV infection.
16. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
17. Major surgery within 3 weeks prior to Randomization.
18. Substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
19. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
One hundred and five (105) study subjects will be randomized 2:1 (INNO-206:doxorubicin) at approximately 30 study centers in the United States (US), Hungary, Romania, Ukraine, Russia, India, and Australia. Up to 32 subjects may be enrolled in India, with the remaining subjects distributed in the other locations.

Test Product, Dose and Mode of Administration:
Lyophilized powder in vials that contain 200 mg of INNO-206 reconstituted by adding a sterile solution of 50% ethanol: 50% water, administration completed within 2 hours (of being reconstituted) as a 30 minute IV infusion in Lactated Ringer's solution. Total dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent).

Reference Therapy, Dose and Mode of Administration:
Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. Prepare IV infusion per the package insert (see the Study Reference Manual).

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:

- Progression-free survival
- Overall survival
- Objective tumor response (RECIST 1.1 criteria)
- 4 and 6 month progression-free survival

Safety:
The following safety variables will be assessed over the duration of the study:

- Adverse events
- Ability to remain on assigned treatment (tolerability)
- Clinical and laboratory data including physical examinations, vital signs, weight, MUGA/cardiac ultrasound evaluations, ECG results and laboratory test results
- Use of concomitant medications

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b

Statistical Methods:

In accordance with the intention-to-treat principle, all randomized subjects who enter active treatment and have had at least 1 dose of study medication and 1 post-dose efficacy measurement will be included in the primary statistical analyses according to the treatment group to which they were originally assigned.

Efficacy:

Tumor response will be monitored every 60 days (2 months) after Cycle 1-Day 1 until Day 240 (8 months) from first drug application (within 5 days of given time point), then every 3 months until disease progression. For the estimation of progression-free and overall survival a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at 4 and 6 months.

Safety:

The safety data will be summarized by treatment group. The treatment groups will be compared with respect to occurrence of each AE. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be compared between groups using Fisher's exact test. Adverse events, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimens. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	End of Treatment[14]	Every 2 or 3 mo.[13]	Follow Up[12]
Signed informed consent	X									
Review inclusion/exclusion	X	X								
Medical history[1]	X									
Physical examination	X	X	X	X	X	X	X	X[16]	X	
Height (cm)	X									
Weight (kg)	X	X	X	X	X	X	X			
BSA calculation[2]		X	X	X	X	X	X			
Vital signs[3]	X	X	X	X	X	X	X	X		
ECOG PS	X	X	X	X	X	X	X	X		
CT/ MRI scan / tumor measurements[4]	X[8a]			X[8]			X[8]	X[10]	X[8]	
ECG	X	X	X	X	X	X	X	X[11]	X	
ECHO (with ejection fraction) or MUGA/cardiac ultrasound	X		X		X		X	X	X	
CBC w/differential & plts[5]	X	X[16]	X	X	X	X	X	X[11]	X	
Serum chemistries [5, 6]	X	X[16]	X	X	X	X	X	X[11]		
Urinalysis[7]	X							X[11]		
Serum troponin	X	X[16]	X	X	X	X	X	X[11]	X	
Serum/urine pregnancy test	X									
Randomization		X[15]								
INNO-206 or doxorubicin admin administration[17]		X	X	X	X	X	X			
Blood alcohol level[18]		X	X	X	X	X	X			
Concomitant medications	X[9]	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X		
Telephone call										X

NOTE: All assessments must be performed within 72 hr of each specified time parameter, except Cycle 1 (see Section 7 for details).

CLINICAL PROTOCOL

TITLE:	**A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma**
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DATE OF PROTOCOL:	**November 14, 2011**
AMENDMENT 1:	**December 16, 2011**
AMENDMENT 2:	**April 15, 2012**

PROTOCOL SIGNATURE PAGE

A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma

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Investigator's Signature: _____

Printed Name: _____

Name of Institution/Company: _____

Date: _____

Sponsor Signature: Daniel Levitt (MD)

Daniel Levitt, M.D., Ph.D.
Chief Medical Officer
CytRx Corporation

Date: April 15, 2012

1. SYNOPSIS

Name of Sponsor/Company: CytRx Corporation	
Protocol Number: INNO-206-P2-STS-01	**Phase of Development:** 2b
Title of the Protocol: A Multicenter, Randomized, Open-Label Phase 2b Study to Investigate the Preliminary Efficacy and Safety of INNO-206 (Doxorubicin-EMCH) Compared to Doxorubicin in Subjects with Metastatic, Locally Advanced, or Unresectable Soft Tissue Sarcoma	
Primary Objectives: The primary objective of this study is to determine the preliminary efficacy of administration of INNO-206 compared to doxorubicin in subjects with metastatic, locally advanced, or unresectable soft tissue sarcoma as measured by progression-free survival, progression-free survival at 4 and 6 months, tumor response and overall survival. **Secondary Objectives:** The secondary objective of this study is to evaluate the safety of INNO-206 compared to doxorubicin in this population assessed by the frequency and severity of adverse events (AEs), abnormal findings on physical examination, laboratory tests, vital signs, multiple-gated acquisition (MUGA) scans/cardiac ultrasound evaluations, electrocardiogram (ECG) results, and weight.	
Study Rationale and Significance: INNO-206 is a novel prodrug that binds covalently to albumin in the circulation. The drug is accumulated in tumors and doxorubicin is released in the tumor by cleaving the acid labile linker (EMCH) in the low pH tumor environment. This carrier-linked prodrug has demonstrated enhanced anti-tumor activity with reduced toxicity in several murine models when compared with free doxorubicin. Patients with metastatic, locally advanced, or unresectable soft tissue sarcomas have a poor prognosis with progression-free survival of around 4-5 months and median overall survival of approximately 15 months. Three-year survival rates as high as 30% have been observed in some clinical studies. Several chemotherapy regimens have been explored as palliative therapy for subjects with advanced soft tissue sarcomas. Combinations of ifosfamide and doxorubicin appear to offer the highest response rates and longest time to progression. However, these regimens are quite toxic and have not significantly increased survival in these individuals. INNO-206 may improve the activity of doxorubicin without increasing its toxicity as has been demonstrated in animal studies.	

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Study Design and Methodology:

This is a phase 2b open-label study evaluating the preliminary efficacy and safety of INNO-206 administered at 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent) intravenously (IV) on Day 1 every 21 days for up to 6 consecutive cycles compared to doxorubicin administered at 75 mg/m^2 for up to 6 consecutive cycles. Subjects will be randomized 2:1 to receive either INNO-206 or doxorubicin.

Subjects will visit the study site every 21 days for their IV infusions, at which time safety monitoring, including AEs, a directed physical examination, laboratory evaluations (serum chemistry, complete blood count [CBC], and urinalysis), vital signs, weight measurements, ECOG performance status and ECGs will be performed. Cardiac function will also be followed periodically using either MUGA scans or cardiac ultrasounds. Treatment will continue every 21 days until tumor progression is observed, 6 cycles of treatment are completed or unacceptable toxicity occurs.

Tumor response will be monitored every 6 weeks from Cycle 1-Day 1 during treatment, at End of Treatment, 2 months following the End of Treatment scan (for those subjects completing 6 cycles), and then every 3 months until disease progression using the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria. For those subjects that leave the study prior to completing Cycle 6, and who do not start another therapy, they can be followed 2 months following the End of Treatment scan, and then every 3 months until disease progression. However, if a subject receives another therapy, they should only be followed for overall survival [OS]. Progression-free survival [PFS], progression-free survival at 4 and 6 months and OS will be monitored as other primary objectives.

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Study Population and Main Criteria for Inclusion/Exclusion:

Inclusion Criteria:

Subjects must meet the following criteria to be included in the study:

1. Age between 15-80 years (US only), and 18-80 (rest of world (ROW)), male or female.
2. Adjuvant or neoadjuvant chemotherapy (including doxorubicin) allowed if no tumor recurrence for at least 12 months since the last measurement, beginning or end of last chemotherapy.
3. Histologically or cytologically confirmed, locally advanced, unresectable, and/or metastatic soft tissue sarcoma of intermediate or high grade.
4. Capable of providing informed consent and complying with trial procedures.
5. ECOG performance status 0-2.
6. Life expectancy >12 weeks.
7. Measurable tumor lesions according to RECIST 1.1 criteria.
8. Women must not be able to become pregnant (eg post-menopausal for at least 1 year, surgically sterile, or practicing adequate birth control methods) for the duration of the study. (Adequate contraception includes: oral contraception, implanted contraception, intrauterine device implanted for at least 3 months, or barrier method in conjunction with spermicide.)
9. Women of child bearing potential must have a negative serum or urine pregnancy test at the Screening Visit and be non-lactating.
10. Geographic accessibility to the site that ensures the subject will be able to keep all study-related appointments.

Exclusion Criteria:

Subjects meeting the following criteria will not be enrolled:

1. Prior chemotherapy unless for adjuvant or neoadjuvant therapy with no tumor recurrence for at least 12 months.
2. Prior exposure to >3 cycles or 225 mg/m^2 of doxorubicin or Doxil®.
3. Palliative surgery and/or radiation treatment less than 4 weeks prior to Randomization.
4. Exposure to any investigational agent within 30 days of Randomization.
5. Current Stage 1 or 2 soft tissue sarcomas.
6. Current evidence/diagnosis of alveolar soft part sarcoma, chondrosarcoma, rhabdomyosarcoma, osteosarcoma, gastrointestinal stromal tumor (GIST), dermatofibrosarcoma, Ewing's sarcoma, Kaposi's sarcoma, mixed mesodermal tumor, clear cell sarcomas and unresectable low grade liposarcomas.
7. Central nervous system metastasis
8. History of other malignancies except cured basal cell carcinoma, superficial bladder cancer or carcinoma in situ of the cervix unless documented free of cancer for $\geq$5 years.
9. Laboratory values: Screening serum creatinine >1.5x upper limit of normal (ULN), alanine aminotransferase (ALT) > 3 × ULN or >5 × ULN if liver metastases are present, total bilirubin >3 × ULN, absolute neutrophil count <1,500/mm^3, platelet concentration <100,000/mm^3, hematocrit level <25% for females or <27% for males, coagulation tests (prothrombin time [PT], partial thromboplastin time [PTT], International Normalized Ratio [INR]) >1.5 × ULN, and albumin <2.0 g/dL.
10. Clinically evident congestive heart failure > class II of the New York Heart Association (NYHA) guidelines.

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11. Current, serious, clinically significant cardiac arrhythmias, defined as the existence of an absolute arrhythmia or ventricular arrhythmias classified as Lown III, IV or V.
12. Baseline QTc >470 msec and/or previous history of QT prolongation while taking other medications. Concomitant use of medications associated with a high incidence of QT prolongation is not allowed
13. History or signs of active coronary artery disease with or without angina pectoris.
14. Serious myocardial dysfunction defined as scintigraphically (eg MUGA, myocardial scintigram) or ultrasound determined absolute left ventricular ejection fraction (LVEF) <45% of predicted.
15. History of HIV infection.
16. Active, clinically significant serious infection requiring treatment with antibiotics, anti-virals or anti-fungals.
17. Major surgery within 3 weeks prior to Randomization.
18. Substance abuse or any condition that might interfere with the subject's participation in the study or in the evaluation of the study results.
19. Any condition that is unstable and could jeopardize the subject's participation in the study.

Number of Subjects:
One hundred and five (105) study subjects will be randomized 2:1 (INNO-206:doxorubicin) at approximately 30 study centers in the United States (US), Hungary, Romania, Ukraine, Russia, India, and Australia. Up to 32 subjects may be enrolled in India, with the remaining subjects distributed in the other locations.

Test Product, Dose and Mode of Administration:
Lyophilized powder in vials that contain 200 mg of INNO-206 reconstituted by adding a solution of 50% ethanol: 50% sterile water, administration completed within 2 hours (of being reconstituted) as a 30 minute IV infusion in Lactated Ringer's solution. Total dose of 350 mg/m^2 (260 mg/m^2 doxorubicin equivalent).

Reference Therapy, Dose and Mode of Administration:
Doxorubicin HCl Injection is a sterile parenteral, isotonic available in 5 mL (10 mg), 10 mL (20 mg), 25 mL (50 mg) single dose vials. Each mL contains doxorubicin HCl and the following inactive ingredients: NaCl (0.9%) and water for injection q.s. Hydrochloric acid is used to adjust the pH to a target of pH of 3.0. Prepare IV infusion per the package insert (see the Study Reference Manual).

Criteria for Evaluation:

Efficacy:
The following efficacy variables will be evaluated as noted:

- Progression-free survival
- Overall survival
- Objective tumor response (RECIST 1.1 criteria)
- 4 and 6 month progression-free survival

Safety:
The following safety variables will be assessed over the duration of the study:

- Adverse events
- Ability to remain on assigned treatment (tolerability)
- Clinical and laboratory data including physical examinations, vital signs, weight, MUGA/cardiac ultrasound evaluations, ECG results and laboratory test results
- Use of concomitant medications

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Statistical Methods:

In accordance with the intention-to-treat principle, all randomized subjects who enter active treatment and have had at least 1 dose of study medication and 1 post-dose efficacy measurement will be included in the primary statistical analyses according to the treatment group to which they were originally assigned.

Efficacy:

Tumor response will be monitored every 6 weeks from Cycle 1-Day1 during treatment, at End of Treatment, 2 months following the End of Treatment scan (for those subjects completing 6 cycles), then every 3 months until disease progression. For the estimation of progression-free and overall survival a Kaplan-Meier analysis will be performed. The percentage of subjects with complete or partial responses, or stable disease will be evaluated at 4 and 6 months.

Safety:

The safety data will be summarized by treatment group. The treatment groups will be compared with respect to occurrence of each AE. Total number of AEs leading to withdrawal, and abnormal laboratory tests will be compared between groups using Fisher's exact test. Adverse events, ability to remain on assigned treatment (tolerability), and abnormal findings on physical examinations, vital signs, weight, ECG results, laboratory test results, and use of concomitant medications, will be assessed to characterize the safety profile of the treatment regimens. Descriptive statistics denoting the changes from baseline to the final assessment visit with respect to key laboratory parameters and vital signs will also be provided.

APPENDIX A: Schedule of Treatment and Evaluations

	Screening -21 Days	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	End of Treatment[14]	Every 2 or 3 mo.[13]	Follow Up[12]
Signed informed consent	X									
Review inclusion/exclusion	X	X								
Medical history[1]	X									
Physical examination	X	X	X	X	X	X	X	X[16]	X	
Height (cm)	X									
Weight (kg)	X	X	X	X	X	X	X			
BSA calculation[2]		X	X	X	X	X	X			
Vital signs[3]	X	X	X	X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	X	X		
CT/ MRI scan / tumor measurements[4]	X[8a]			X[8]		X[8]		X[10]	X	
ECG	X	X	X	X	X	X	X	X[11]	X	
ECHO (with ejection fraction) or MUGA/cardiac ultrasound	X		X		X		X	X	X	
CBC w/differential & plts[5]	X	X[16]	X	X	X	X	X	X[11]	X	
Coagulation tests (PT, PTT, INR)	X									
Serum chemistries[5, 6]	X	X[16]	X	X	X	X	X	X[11]		
Urinalysis[7]	X							X[11]		
Serum troponin	X	X[16]	X	X	X	X	X	X[11]	X	
Serum/urine pregnancy test	X									
Randomization		X[15]								
INNO-206 or doxorubicin admin administration[17]		X	X	X	X	X	X			
Blood alcohol level[18]		X	X	X	X	X	X			
Concomitant medications	X[9]	X	X	X	X	X	X	X		
Adverse events	X	X	X	X	X	X	X	X		
Telephone call										X

NOTE: All assessments must be performed within 72 hr of each specified time parameter, except Cycle 1 (see Section 7 for details).