Moleculin Biotech, Inc.

CLINICAL STUDY REPORT

Phase 1/2 Study of Liposomal Annamycin for the Treatment of Subjects With Acute Myeloid Leukemia (AML) That is Refractory to or Relapsed After Induction Therapy

Test Product: Liposomal Annamycin

Protocol Number:	MB-105
EudraCT Number:	2017-003969-10
Sponsor:	Moleculin Biotech, Inc. 5300 Memorial Drive Suite 950 Houston, TX, 77070
Principal Investigators:	Prof. Lidia Gil, (MD, PhD) Szpital Kliniczny Przemienienia Pańskiego Uniwersytetu Medycznego im. Karola Marcinkowskiego Poznań, Poland Prof. Agnieszka Wierzbowska, (MD, PhD) Wojewódzki Szpital Specjalistyczny im. M. Kopernika Łódz, Poland Prof. Tomasz Wróbel, (MD, PhD) Uniwersytecki Szpital im. Jana Mikulicza Wrocław, Poland Prof. Ewa Lech-Marańda, (MD, PhD) Instytut Hematologii i Transfuzjologin Warszawa, Poland Prof. Bogulsaw Machaliński, (MD, PhD, DSc) Samodzielny Publiczny Szpital Kliniczny nr 1, im. Prof. Tadeusza Sokołowskiego w Szczecinie Pomorski Uniwersytet Medycsny – Szczecin, Poland
Medical Monitor:	Theradex® 4365 Route 1 South Suite 101 Princeton, NJ, 08540
Study Initiation Date: (First Subject On-Study)	08 February 2019
Study Completion Date: (Last Subject Last Visit)	14 February 2022
Date of Clinical Study Report:	13 January 2023

This study was performed in compliance with the principles of Good Clinical Practice (ICH E6 R2), including the archiving of essential documents. This report complies with ICH Guideline E3.

2 SYNOPSIS

<table>
<tr><td>Name of Sponsor:

Moleculin Biotech, Inc.</td><td rowspan="3">Individual study table referring to part of the dossier

Volume:

Page:</td><td rowspan="3">(For national authority use only)</td></tr>
<tr><td>Name of finished product:

Liposomal Annamycin</td></tr>
<tr><td>Name of active ingredient:

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<tr><td colspan="3">Title of the study:

Phase 1/2 Study of Liposomal Annamycin for the Treatment of Subjects With Acute Myeloid Leukemia (AML) That is Refractory to or Relapsed After Induction Therapy</td></tr>
<tr><td colspan="3">Principal/Coordinating Investigator name, number of study centers and countries:

This was a multi-center study conducted at five sites in Poland.

The Principal National Coordinating Investigator was Professor Lidia Gil, (MD, PhD), Karol Marcinkowski Medical University, Poznań.</td></tr>
<tr><td colspan="3">Publication (references):

Not applicable</td></tr>
<tr><td colspan="2">Study period (years):

First subject on-study date: 08 February 2019

Study completion date: 14 February 2022</td><td>Clinical phase:

Phase 1/2</td></tr>
<tr><td colspan="3">Objectives:

<u>Primary objective:</u>

• To evaluate the safety and identify the recommended Phase 2 dose (RP2D) of liposomal annamycin (L-Annamycin) for the treatment of subjects with AML that is refractory to or relapsed after induction therapy.

<u>Secondary objectives:</u>

• Pharmacokinetics of L-Annamycin and its metabolite, annamycinol

• Preliminary assessment of the antileukemic activity of L-Annamycin as second line (or subsequent) therapy for subjects with refractory or relapsed AML on the basis of established response criteria, including complete response (CR), CR with incomplete recovery of platelets and/or neutrophils (CRi), partial response (PR), event-free survival (EFS), overall survival (OS), and time to and duration of response.</td></tr>
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Methodology:

This was a multicenter, open-label, dose-escalation study to determine the maximum tolerated dose (MTD) and RP2D of L-Annamycin as a single agent for the treatment of subjects with AML that was refractory to or relapsed after induction therapy.

Enrolment was to occur in cohorts of three subjects in a conventional 3+3 escalating dose design, starting at a dose level of 120 mg/m^2/day administered for three consecutive days. Dose escalation was to take place on the basis of safety assessments in sequential cohorts of three subjects each. In the absence of dose-limiting toxicities (DLTs), dose escalation by 30 mg/m^2/day increments was to continue in subsequent cohorts until an MTD was reached. Thus, subsequent cohorts were to receive 150, 180, 210, 240, 270, 300, and up to 330 mg/m^2/day of L-Annamycin for three days in the absence of safety concerns However, if one of the three initial subjects experienced a DLT, the cohort of subjects at that dose level was to be expanded to six subjects. If at least two of the six subjects experienced a DLT, this was to be considered a toxic dose and the next three subjects were to be treated at a lower dose. The dose was to be de-escalated by 15 mg/m^2/day. If one of the three initial subjects experienced a DLT at the lowered dose, the cohort of subjects was to be expanded to six subjects. If at least two of the six subjects experienced a DLT, this was to be considered a toxic dose.

After determination of the MTD (defined as the highest dose of L-Annamycin at which fewer than two of a cohort of up to six subjects experienced a DLT) and the RP2D (defined as the optimal dose to be explored in the expansion phase portion of the study as determined by the Sponsor on the basis of review of available clinical and laboratory safety and efficacy data), up to 21 additional subjects were to be enrolled at either the MTD or RP2D to better define toxicity and evaluate efficacy at this dose.

Number of subjects (planned and analyzed):

Approximately 75 subjects were to be enrolled in this study: up to 54 subjects in the dose-escalation phase and up to 21 additional subjects at the MTD or RP2D.

Overall, this study enrolled 20 subjects in the dose-escalation phase, all of whom received treatment with L-Annamycin. Of the 20 subjects treated, nine subjects were male, and 11 subjects were female, with an age demographic of between 24 and 76 years. The study was terminated early during the dose-escalation phase as preclinical animal data demonstrated that L-Annamycin in combination with cytarabine led to a significant improvement in median overall survival compared to either L-Annamycin or cytarabine administered as single agents. As such, the Sponsor ceased single-agent development of L-Annamycin in favor of evaluating L-Annamycin in combination with cytarabine.

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Diagnosis and Main Criteria for Inclusion and Exclusion:

Subjects were male or female, aged ≥18 years, with a pathologically confirmed diagnosis of AML that was refractory to or relapsed after induction therapy.

Subjects were required to have adequate laboratory results and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. Female subjects of childbearing potential had to have a negative pregnancy test at screening and all subjects had to agree to practice effective contraception throughout treatment and for defined periods after their last dose.

Subjects could not participate in the study if they had received chemotherapy, radiation, major surgery (unless recovered from the toxic side effects of any previous therapy) or other investigational therapies within specific timeframes prior to first dose, if they were diagnosed with acute promyelocytic leukemia, if they were receiving concomitant therapy that would have been active against AML, if they had central nervous system involvement, if their cardiac function did not meet specified conditions, if they had clinically relevant serious comorbid medical conditions, if they had an allergy to anthracyclines, if they had ongoing Grade 1 mucositis, or if they had any other condition which, in the opinion of the Investigator, made them unsuitable for the study.

A full list of the inclusion and exclusion criteria for the study is presented in Section 9.3.

Test product, dose and mode of administration, batch numbers:

Annamycin is a lipophilic anthracycline antibiotic that incorporates four structural modifications from doxorubicin: 2'-iodo, 3'-hydroxy, 4'-epi, 4-demethoxy doxorubicin. It was developed at MD Anderson Cancer Center and supplied by Moleculin Biotech, Inc.

The test product was to be provided as a lyophilized powder in 50 mL vials and was to be reconstituted prior to use. The reconstituted L-Annamycin suspension was to be administered via intravenous (IV) infusion for which a peripheral vein could be used. All subjects were to receive tumor lysis syndrome prophylaxis as well as oral cryotherapy and mouthwash prophylaxis for mucositis, and antiallergic premedication with an antihistamine was to be administered before each dose of L-Annamycin.

The starting dose of L-Annamycin was 120 mg/m^2/day. Dose escalation was to occur in 30 mg/m^2/day increments in the absence of DLTs.

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Five batches of L-Annamycin were used in this study. The batch numbers (and associated lot numbers) were:

- 16192
- S18L031 – Associated lot numbers: E180251-0015L001, E180251-0015L002, E180251-0015L003, E180251-0015L004, E180251-0015L005, E180251-0017L001
- S19A008 – Associated lot numbers: E180251-0016L001, E180251-0016L002, E180251-0016L003, E180251-0016L005, E180251-0016L009
- S19I014 – Associated lot numbers: E180251-0018L002, E180251-0018L003, E180251-0018L006, E180251-0018L008, E180251-0018L010
- S20E022 – Associated lot number: E180251-0019L003.

Duration of treatment:

All subjects were to receive one initial cycle of L-Annamycin lasting 21 days and comprising three consecutive days of daily IV infusions followed by 18 days off study drug. An end of study (EOS) visit was to be conducted one week after the end of the initial cycle, and safety and survival follow-up visits were to take place every three months thereafter.

A subject could receive one additional cycle of L-Annamycin after the end of the initial cycle if the subject experienced a near-CR after completion of the initial cycle.

Criteria for evaluation:

Safety:

1. Clinical adverse events (AEs), routine hematological and biochemical parameters, physical examination and vital signs (blood pressure, pulse, respiratory rate, and body temperature), 12-lead electrocardiograms (ECGs), ECOG performance status, pregnancy testing, and monitoring of concomitant medications were to be assessed according to the Schedule of Events (Section 9.5.1).
2. All AEs and laboratory abnormalities were to be graded for severity by using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5. The relatedness of all AEs and laboratory abnormalities and their seriousness were to be determined by the Investigator and adjudicated by the Sponsor.
3. AEs were to be documented from the time of the first dose of study drug until 30 days after the last dose administered on study for the initial cycle and until 32 days after the last administration of the study drug for the subsequent cycle (if administered). AEs were also to be documented every three months (± one month) thereafter for all subjects who completed

the EOS visit or until a subject received a therapy that was not the study drug during either cycle. Any AEs that occurred after Day 21 during either cycle were not to be evaluated as DLTs.

Strategies for detection of cardiotoxicity were to include cardiac imaging (echocardiography, nuclear imaging, cardiac magnetic resonance) and assessment of cardiac biomarkers (troponin-I and troponin-T).

Efficacy:

Primary Efficacy Endpoints:

1. CR:
   a. Achievement of normal bone marrow morphology on light microscopy with fewer than 5% blasts
   b. Recovery of peripheral blood counts with an absolute neutrophil count $>1.0 \times 10^9$/L and platelet counts $>100 \times 10^9$/L
2. CRi: CR with incomplete recovery of platelets and/or neutrophils
3. PR: a ≥50% decrease in marrow blasts
4. Subject deemed eligible for hematopoietic stem cell transplantation

Secondary Efficacy Endpoints:

1. EFS: Time from enrollment until disease progression or death from any cause
2. OS: Time from enrollment until death from any cause
3. Time to and duration of response
4. Cytogenetic CR – cytogenetics normal in those with previously abnormal cytogenetics

Pharmacokinetics:

The pharmacokinetics of L-Annamycin and its metabolite, annamycinol, were to be determined. Blood samples for pharmacokinetic (PK) analysis were to be collected at predose and at 0.25, 0.5, 1, 2, 4, 8, and 24 hours after the start of L-Annamycin infusion on Day 1 and Day 3 during the initial cycle only for three subjects at each dose and six subjects at the RP2D who completed the three days of dosing.

Statistical methods:

Only descriptive statistics were to be utilized for this study.

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Safety and tolerability were to be assessed by AEs, vital signs, physical examination, laboratory parameters, and multiple-gated acquisition or echocardiogram (ECHO) scans or ECHO strain evaluations, as well as cardiotoxicity biomarkers (troponin-I and troponin-T). AEs were to be listed by subject and were to be tabulated and summarized as the number and percentage of subjects who reported each AE. Descriptive statistics were to be generated as appropriate; no other formal statistical analyses were planned on the safety data.

PK parameters (maximum concentration, area under the time-concentration curve, elimination half-life, volume of distribution, and clearance) were to be calculated for L-Annamycin and its metabolite, annamycinol, on the basis of plasma concentrations. PK data were to be analyzed with descriptive statistics as appropriate.

ECGs and documentation of concomitant medications affecting cytochrome P450 family of enzymes were to be obtained to ensure that these were a consideration in the evaluation of the safety and pharmacokinetics of this drug.

Summary of results and conclusions:

Safety Results:

- All 20 subjects enrolled (100.0%) received at least one dose of treatment, comprising the safety-evaluable population.
- All 20 subjects (100.0%) experienced at least one treatment-emergent adverse event (TEAE) of any severity grade.
- All 20 subjects (100.0%) experienced at least one drug-related TEAE.
- Overall, 18 subjects (90.0%) experienced at least one severe TEAE (Grade ≥3).
- A total of 15 subjects (75.0%) experienced at least one drug-related severe TEAE.
- A total of 17 subjects (85.0%) experienced at least one serious adverse event (SAE) in the study.
- A total of 11 subjects (55.0%) experienced at least one SAE that was possibly, probably or definitely related to study drug.
- Four subjects (20.0%) experienced at least one TEAE leading to dose interruption, including TEAEs where additional actions were taken.
- Three subjects (15.0%) experienced at least one TEAE leading to dose delayed.
- One subject (5.0%) had a TEAE leading to dose reduction on the study, but the overall action taken for the event was reported as dose interrupted.
- Three subjects (15.0%) experienced at least one TEAE leading to drug withdrawal.
- No DLTs were observed during the study.

- Two subjects (10.0%) experienced TEAEs leading to death, including one TEAE of corona virus infection (Grade 5) and one TEAE of multiple organ dysfunction (Grade 5), both assessed as unrelated to study drug.
- No evidence of cardiac toxicity was identified. Both cardiac enzyme concentrations (troponins) and left ventricular ejection fraction (LVEF) remained stable throughout the study in all subjects. All ECHO recordings were submitted to a central laboratory (Duke University School of Medicine; Cardiac Diagnostic Unit ECHO Core Lab) for strain analyses. Furthermore, all cardiac safety data collected on the MB-105 study were sent to an expert in assessing chemotherapy-related cardiotoxicity at the Cleveland Clinic. This included the LVEF and troponin data noted above, in addition to the ECHO strain report(s) provided by Duke's ECHO Core Lab. Independent review of the cardiac safety data confirmed that there was no evidence of cardiotoxicity in any subject treated on this study, including up to 16 subjects whose cumulative anthracycline dose (L-Annamycin included) exceeded the lifetime cumulative doxorubicin (or equivalent) dose of >450 mg/m^2. To that end, the cardiac toxicity, seen with other anthracyclines, has not yet been identified with L- Annamycin.

Efficacy Results:

- Efficacy results were provided for both the intent-to-treat analysis set and the efficacy-evaluable analysis set.
- Of the 20 subjects enrolled, 17 subjects (85.0%) received at least three doses of L-Annamycin per protocol and had at least one post-treatment AML response assessment, comprising the efficacy-evaluable population.
- Of the 20 intent-to-treat subjects:
  - One subject (5.0%) had a CRi
  - Three subjects (15.0%) had a PR
  - All responders were in the 240 mg/m^2/day treatment arm
  - Sixteen subjects (80.0%) experienced treatment failure
- Of the 17 efficacy-evaluable subjects:
  - One subject (5.9%) had a CRi
  - Three subjects (17.6%) had a PR
  - Thirteen subjects (76.5%) experienced treatment failure

Pharmacokinetic Results:

- The exposure of annamycin and annamycinol for Day 1 and Day 3 were similar within the dose level and increased with increasing dose. The median time to maximum plasma concentration was similar across dose levels.

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Conclusions:

Administration of L-Annamycin to subjects with relapsed or refractory AML was found to:

- Be reasonably tolerated at 120, 150, 180, 210, and 240 mg/m^2/day for three consecutive days, with one suspected unexpected serious adverse reaction (infusion-related reaction) reported in the final cohort (240 mg/m^2/day). Reported SAEs were medically manageable and aligned with clinical safety observations in prior and ongoing clinical studies.
- Demonstrate no evidence of cardiotoxicity based on review of cardiotoxicity biomarkers, LVEF, and ECHO strain evaluation.
- Demonstrate promising preliminary efficacy results in the 240 mg/m^2/day cohort as a single agent that, taken together with preclinical animal data exploring L Annamycin in combination with cytarabine, supports the continued development of L Annamycin in this subject population.

Date and version of this report:

13 January 2023, Version 1.0

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S)

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STUDY AUTHOR: Moleculin Biotech, Inc.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

NATIONAL CHIEF COORDINATOR: Prof. Lidia Gil (MD, PhD)

SIGNATURE: L. Gil

AFFILIATION: Szpital Kliniczny Przemienienia Pańskiego
Uniwersytetu Medycznego im. Karola Marcinkowskiego
Poznań, Poland

Uniwersytecki Szpital Kliniczny (ss)
w Poznaniu
60-355 Poznań, ul. Przybyszewskiego 49
Regon 000289534, NIP 779-20-33-466
ODDZIAŁ HEMATOLOGII I TRANSPLANTACJI SZPIKU
60-569 Poznań, ul. Szamarzewskiego 84
tel. 61 854 93 83
0000000185731(I)-12(V)-243(V II)-4070(VIII)

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