SYNOPSIS OF RESEARCH REPORT 1043178 (PROTOCOL WN25333)

COMPANY: NAME OF FINISHED PRODUCT: NAME OF ACTIVE SUBSTANCE(S):	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY / REPORT No. / DATE OF REPORT	Final Clinical Study Report – WN25333 (CandleLyte). A phase II/III, multi-center, randomized, 4-week, double-blind, parallel group, placebo and active controlled trial of the safety and efficacy of bitopertin vs. placebo in patients with acute exacerbation of schizophrenia. Report No. 1043178, Version 1: August 2013. Version 2: July 2014.
INVESTIGATORS / CENTERS AND COUNTRIES	Romania (3 sites), Russia (9), Slovakia (4), Ukraine (5), and the USA (15). ***Version 2 Change:*** *The List of Facilities was replaced by a detailed List of Investigators and study sites. This change did not have any impact on the overall results and conclusions of the study.*
PUBLICATION (REFERENCE)	None
PERIOD OF TRIAL	15 February 2011 - 10 September 2012
CLINICAL PHASE	II/III
OBJECTIVES	**Primary Objectives** • The efficacy of 4-week treatment with bitopertin versus placebo on symptoms of schizophrenia as measured by the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score • The safety and tolerability of 4-week treatment with bitopertin versus placebo in patients with acute symptoms of schizophrenia. **Secondary Objectives** The secondary objectives of the study were to evaluate efficacy of bitopertin versus placebo in the following at Week 4: • Clinical response (at least 30% or 50% improvement from baseline on PANSS total score) • Change in symptomatology as measured by the PANSS factor and subscale scores • Global improvement as measured by the rating on the Clinical Global Impression of Change (CGI-C) scale • Global improvement as measured by the change from baseline in the Clinical Global Impression – Severity of Illness (CGI-S) score

	• Observable behavioral change as determined by the Nurses' Observation Scale For Inpatient Evaluation (NOSIE) • Time to readiness for discharge from the in-patient unit as assessed by the Readiness for Hospital Discharge Questionnaire (RDQ). **<u>Exploratory Objectives</u>** The exploratory objectives of the study were to evaluate the effect of treatment with bitopertin in patients with an acute exacerbation of schizophrenia with respect to: • Changes in overall functioning as measured by the change from baseline in Personal and Social Performance (PSP) scale total score at Week 4 • Medication satisfaction during the double-blind period as assessed by the Medication Satisfaction Questionnaire (MSQ) at Week 4 • The pharmacokinetics in the target population and the influence of co-variates on the pharmacokinetics of bitopertin • Biomarker and pharmacogenomic properties.
STUDY DESIGN	This was a Phase II/III, multi-center, randomized, 4-week, double-blind, double dummy, parallel group, placebo and active-controlled trial to evaluate the safety and efficacy of bitopertin versus placebo in patients with an acute exacerbation of schizophrenia. The total duration of the study for each patient was approximately 9 weeks divided as follows: • Screening period up to 14 days • 4-week inpatient double-blind treatment period • 4-week follow-up period without study treatment Following screening, patients were randomized to one of the four monotherapy treatment arms: bitopertin 10 mg, bitopertin 30 mg, olanzapine 15 mg, or placebo once daily. All participants remained inpatients throughout the entire 4-week double-blind period, and completed visit assessments, including any assessments in situations of premature study withdrawal.
NUMBER OF SUBJECTS	300 (planned), 301 (randomized)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Patients aged 18-65 recently hospitalized with an acute exacerbation of schizophrenia.
TRIAL DRUG / STROKE (BATCH) No.	Bitopertin 10 mg: [redacted] Bitopertin 20 mg: [redacted] Placebo: [redacted]
DOSE / ROUTE / REGIMEN / DURATION	Tablets of bitopertin 10 mg and 20 mg or placebo to provide bitopertin doses of 0, 10 mg or 30 mg orally once a day
REFERENCE DRUG / STROKE (BATCH) No.	Olanzapine 15 mg: [redacted] Placebo: [redacted]

DOSE / ROUTE / REGIMEN / DURATION	Olanzapine 15 mg capsule orally once a day
CRITERIA FOR EVALUATION	
EFFICACY:	Primary: PANSS Total Score Secondary: • Percent responders on the PANSS and on the CGI-C • PANSS subscales and factor scores • CGI-S • NOSIE • RDQ Exploratory: Roche Clinical Repository (RCR) non-DNA blood and serum specimen(s) were taken from consenting patients at baseline and week 4. All patients were asked to donate an optional DNA specimen for pharmacogenetic and genetic research. RCR DNA sampling involved taking a blood sample at baseline. Specimens for protein biomarker discovery and validation were collected from all patients.
PHARMACODYNAMICS:	N/A
PHARMACOKINETICS:	Plasma concentrations of bitopertin
SAFETY:	• Adverse events • Blood pressure, heart rate, weight, electrocardiogram (ECG), physical examination, visual acuity • Columbia Suicide Severity Rating Scale (C-SSRS) • Extrapyramidal Symptoms Rating Scale – Abbreviated version (ESRS-A) • Blood and urine safety laboratory assessments, drug screen, pregnancy tests
STATISTICAL METHODS	For all analyses of PANSS data, the scores were transformed into 0 – 6 points to express “absent” as 0. The efficacy parameters of continuous variables with more than one post-baseline assessment were analyzed using a mixed effects model repeated measure (MMRM) method to utilize all the data collected over time with consideration of the variance-covariance matrix of the repeated measures. The model included independent variables of the fixed, categorical effects of treatment, assessment weeks (i.e., time), and treatment-by-time interaction, and a covariate of the baseline value. As a supportive analysis, the primary efficacy variable was also analyzed for the Week 4 assessment by analysis of covariance (ANCOVA) adjusting for baseline values, using the observed cases and last observation carried forwarded (LOCF) values. The model included the baseline measure as covariate and treatment as main effect. The efficacy parameters of continuous variables with only one post-baseline assessment were analyzed using the ANCOVA model described above. Categorical data, such as the percentage of responders, was evaluated by the Cochran-Mantel-Haenszel (CMH) with the geographical region of study centers and duration of illness as stratification factors.

	The time-to-readiness for discharge from in-patient unit was analyzed using an un-stratified log rank test. In addition, a stratified log rank test of treatment difference was performed with region and duration of illness as stratification factors.

METHODOLOGY

Following informed consent, patients who met study criteria completed screening assessments (up to 2 weeks), followed by a four week inpatient double blind treatment period during which patients were randomized to one of the four treatment arms: bitopertin 10 mg, bitopertin 30 mg, olanzapine 15 mg, or placebo once daily. During the double blind treatment period, patients were assessed at baseline, Day 4, and at Weeks 1-4; assessments included the PANSS, CGI, NOSIE, MSQ (except on Day 4), RDQ, PSP (at baseline and week 4 only), and safety parameters. The double blind treatment period was followed by a four week period were patients could remain in the hospital until stable on a maintenance medication for schizophrenia.

EFFICACY RESULTS

Primary Efficacy Endpoint

The key efficacy findings are summarized in Table 1. The extent of the decrease from baseline to Week 4 in PANSS total score was greater in the bitopertin 30 mg (−15.25) and olanzapine (−14.90) treatment arms compared with the placebo arm (−11.91). These differences did not reach statistical significance (bitopertin 30 mg p=0.2113; olanzapine p=0.2952). The decrease from baseline to Week 4 in the bitopertin 10 mg arm was similar to that in the placebo arm (−11.72 vs. −11.31, p=0.9445).

Similar results were observed in the supportive ANCOVA analysis of ITT population at Week 4 LOCF and ANCOVA analysis of observed case data at Week 4.

Secondary Efficacy Endpoints

Improvements were observed on the CGI-S, the PANSS positive subscale, and the PANSS uncontrolled hostility/excitement factor score in both the bitopertin 30 mg and the olanzapine groups. In addition, more patients on bitopertin 30 mg (55%) and olanzapine (54%) than placebo (35%) were ready for discharge during the study, and were ready earlier. The other secondary assessments showed no remarkable differences between the active treatment arms and placebo.

Table 1 Overview of Primary and Secondary Efficacy Endpoints at Week 4 (ITT Population)

	Placebo (N = 79)	Bitopertin 10mg (N = 77)	Bitopertin 30mg (N = 76)	Olanzapine (N = 61)
Primary Efficacy Endpoint				
PANSS Total Score [a,1]	-11.91 (1.897)	-11.72 (1.891)	-15.25 (1.870)	-14.90 (2.128)
Secondary Efficacy Endpoints				
PANSS responders No (%)				
30% [b,2] (LOCF)	25 (31.6%)	23 (29.9%)	32 (42.1%)	19 (31.1%)
50% [b,2] (LOCF)	3 (3.8%)	5 (6.5%)	9 (11.8%) [#]	5 (8.2%)
PANSS subscales and Marder factor scores [a,1]				
PANSS PS	-3.73 (0.626)	-3.95 (0.624)	-5.66 (0.616) [*]	-5.44 (0.702) [#]
PANSS NS	-2.11 (0.462)	-1.91 (0.460)	-2.90 (0.453)	-2.70 (0.517)
PANSS GPS	-6.62 (1.004)	-6.51 (1.000)	-6.95 (0.985)	-7.09 (1.124)
PANSS PSFS	-4.76 (0.671)	-4.13 (0.670)	-5.89 (0.663)	-5.46 (0.753)
PANSS NSFS	-2.32 (0.492)	-2.43 (0.491)	-2.49 (0.483)	-3.08 (0.552)
PANSS DTCFS	-2.08 (0.441)	-2.38 (0.440)	-3.09 (0.432)	-2.46 (0.494)
PANSS UHEFS	-0.79 (0.408)	-1.07 (0.406)	-1.77 (0.400) [#]	-2.09 (0.457) [*]
PANSS ADFS	-2.70 (0.418)	-2.70 (0.416)	-2.49 (0.409)	-2.33 (0.468)
CGI-S [a,1]	-0.68 (0.123)	-0.72 (0.122)	-0.96 (0.120) [#]	-0.96 (0.137)
CGI-C responders [c,2] (LOCF) No (%)	19 (24.1%)	27 (35.1%)	23 (30.3%)	26 (42.6%) [*]
NOSIE total assets score [1]	4.37 (1.944)	6.48 (1.940)	4.94 (1.918)	6.79 (2.180)
RDQ				
Patients with event [d] No (%)	28 (35.4%)	33 (42.9%)	42 (55.3%)	33 (54.1%)
Median Time to event (95% CI, days) [3,4]	28 (27,)	28 (27,)	27 (27, 28) [#]	28 (26, 28)

PS: positive subscale, NS: negative subscale, GPS: general psychopathology subscale, PSFS: positive symptoms factor score, NSFS: negative symptoms factor score, DTCFS: disorganized thoughts/cognition factor score, UHEFS: uncontrolled hostility/excitement factor score, ADFS: anxiety/depression factor score, CGI-S: Clinical Global Impression – Severity of Illness, CGI-C: Clinical Global Impression of Change, NOSIE: Nurses' Observation Scale for Inpatient Evaluation, RDQ: Readiness for Hospital Discharge Questionnaire.

Difference from placebo: # unadjusted $0.05 < p \leq 0.1$, * unadjusted $p \leq 0.05$.

[a] Assessed by site raters.

[b] PANSS responder (30% or 50%) is defined as a 30% or greater or 50% or greater improvement in PANSS total score.

[c] CGI-C responder is defined as patient with a rating of either "much" or "very much" improvement.

[d] Readiness for discharge from the in-patient unit.

[1] Adjusted mean change from baseline and SE are presented. Analysis is based on MMRM using unstructured covariance matrix: Change = Baseline + Week + Treatment + Treatment*Week (repeated values over Week).

[2] Analysis is based on Cochran-Mantel-Haenszel test with region and duration of illness as stratification variables.

[3] Kaplan-Meier estimate.

[4] Analysis is based on log rank test.

PHARMACODYNAMIC RESULTS

N/A

PHARMACOKINETIC RESULTS

Will be reported separately.

SAFETY RESULTS

Four-Week Treatment Period

An overview of AEs during the treatment period is provided in Table 2. Bitopertin at doses of 10 mg and 30 mg per day for four weeks was generally safe and well-tolerated.

Table 2 Overview of Adverse Events During the Treatment Period

Protocol(s): WN25333 (I25333V)
Population: Safety-Evaluable Patients
Subset: AEs During the Treatment Period

	Placebo (N=80)	RO4917838 10mg (N=80)	RO4917838 30mg (N=77)	Olanzapine (N=62)
Total number of patients with at least one AE	47 (58.8%)	43 (53.8%)	52 (67.5%)	37 (59.7%)
Total number of AEs	125	102	145	91
Total number of patients with at least one				
Serious AE	0	0	3 (3.9%)	1 (1.6%)
AE leading to withdrawal from treatment	4 (5.0%)	8 (10.0%)	10 (13.0%)	4 (6.5%)
Severe AE (at highest intensity)	3 (3.8%)	4 (5.0%)	4 (5.2%)	3 (4.8%)
Total number of patients with AEs of special interest:				
Suicidality*	1 (1.3%)	0	1 (1.3%)	0
Mood changes*	1 (1.3%)	3 (3.8%)	2 (2.6%)	1 (1.6%)
Visual findings*	0	0	0	1 (1.6%)
Skin findings*	1 (1.3%)	2 (2.5%)	1 (1.3%)	0
Suicide/self-injury (SMQ 20000037 narrow)	1 (1.3%)	0	1 (1.3%)	0

Includes AEs with onset or worsening from the day of first dose of study drug through the day of last dose of study drug.
Investigator text for AEs encoded using MedDRA version 15.0. Percentages are based on N in the column headings.
For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once.
For frequency counts in the "Total number of AEs" row, multiple occurrences of the same AE in an individual are counted separately.
Note: There are no patients who died or experienced events of abuse liability during the treatment period.
* Reported by investigator.

Program: /opt/BIOSTAT/prod/cdt4715c/aet001.sas
Output: /opt/BIOSTAT/prod/cdt4715c/i25333v/reports/aet001_SE_TP.out
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No patient died during the study and there were a total of four SAEs during the treatment period: three in the bitopertin 30 mg arm and one case in the olanzapine arm. Only one SAE in the bitopertin 30 mg arm (psychotic disorder) was reported to be (remotely) related to the study drug by the investigator. This SAE resolved without sequelae.

There were more patients with AEs that led to permanent discontinuation of the study medication in the bitopertin 30 mg arm (14.3%) compared with the other arms (6.3% on placebo, 10.0% on bitopertin 10 mg and 9.7% on olanzapine). The most common AEs leading to discontinuation belonged to the body system organ class of psychiatric disorders, most frequently schizophrenia and psychotic disorder.

During the treatment period, a greater proportion of patients in the bitopertin 30 mg arm (67.5%) experienced at least one AE compared with bitopertin 10 mg (53.8%), placebo (58.8%) and olanzapine (59.7%). The most common AEs reported in both bitopertin arms were headache (8.8% and 11.7% in bitopertin 10 mg and 30 mg dose groups, respectively, compared with 6.3% on placebo and 6.5% on olanzapine) and insomnia (8.8% and 13.0% in 10 mg and 30 mg dose groups, respectively, compared with 11.3% on placebo and 8.1% on olanzapine). Somnolence was the most common AE reported in the olanzapine arm (11.3%) and occurred more frequently compared with the other arms (7.5% on placebo, 1.3% and 6.5% on bitopertin 10 mg and 30 mg, respectively).

Most AEs were mild or moderate in intensity. Overall, intensity of AEs was similar between treatment arms.

There were similar numbers of AEs of special interest/selected AEs (suicidality, visual findings, skin findings, mood changes and extrapyramidal syndrome) reported between treatment arms.

A gradual, dose-dependent reduction in hemoglobin between baseline and Week 4 was observed in the bitopertin arms. No patient was withdrawn from the study due to low hemoglobin levels.

No other clinically relevant changes in laboratory parameters indicative of any treatment-emergent effect were observed during the study. There were no clinically relevant changes in vital signs, ECG parameters and weight observed in the bitopertin arms. Increased body weight was observed in the olanzapine arm.

No clinically relevant differences in safety profile were observed between CFHR1 high and low subgroups.

Safety During the Follow-up Period

During the follow-up period, there were fewer AEs reported in the bitopertin arms compared with the placebo and the olanzapine arms mainly due to a lower incidence of psychiatric and nervous system disorders. No indication of withdrawal symptoms during the follow-up period was observed.

CONCLUSIONS

No definitive conclusions could be drawn on the efficacy of 4-week treatment with bitopertin on symptoms of schizophrenia as measured by the primary endpoint, the change from baseline in the PANSS total score, because the difference between the active control (olanzapine) and placebo failed to reach statistical significance. Similar improvements in the PANSS total score were observed in the olanzapine and bitopertin 30 mg arms. The change observed in the bitopertin 10 mg arm was similar to that in the placebo arm..

Some of the endpoints suggested a favorable effect of bitopertin 30 mg compared to placebo in acute psychosis: CGI-S, PANSS positive subscale factor score, PANSS uncontrolled hostility/excitement factor score, and RDQ time to discharge.

Bitopertin at doses of 10 mg and 30 mg per day for four weeks was generally safe and well-tolerated, and the safety profile was consistent with previous studies.