STATISTICAL ANALYSIS PLAN

PROTOCOL: DLP-114-03

Open-Label Study in Stable Schizophrenia Patients to Evaluate the Safety, Tolerability, and Pharmacokinetics of Switching from Oral Risperidone to Risperidone Implant (DLP-114)

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PRODUCT : DLP-114

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DATE: 13 June 2022

STATUS: Final Version 1.0

Statistical Analysis Plan
Protocol: DLP-114-03
Final Version: 1.0 Date: 14 JUN 2022

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AMENDMENT HISTORY

Not applicable

LIST OF ABBREVIATIONS

AE	Adverse Event
AIMS	Abnormal Involuntary Movement Scale
ALT	Alanine aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate aminotransferase
BARS	Barnes Akathisia Rating Scale
BLQ	Below the limit of quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CGI-I	Clinical Global Impression Scale – Improvement
CGI-S	Clinical Global Impression Scale – Severity
C-SSRS	Columbia-Suicide Severity Rating Scale
ECG	Electrocardiogram
CRF	Case Report Form
EPS	Extrapyramidal Symptoms
ET	Early Termination
GGT	Gamma glutamyl transferase
HbA1c	Hemoglobin A1c
HbsAg	Hepatitis B surface antigen
HCV	Hepatitis C antibodies
HDL	High density lipoprotein
HIV	Human Immunodeficiency Virus
INR	International Normalized Ratio
LDH	Lactic Acid Dehydrogenase
LDL	Low Density Lipoprotein
MedDRA	Medical Dictionary of Regulatory Activities
PANSS	Positive and Negative Syndrome Scale
PK	Pharmacokinetic
PT	Prothrombin Time
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	Serious Adverse Event
SAS	Simpson-Angus Scale

1 INTRODUCTION

This statistical analysis plan (SAP) describes the final statistical analysis for patient information and safety data to be performed for the study entitled “Open-Label Study in Stable Schizophrenia Patients to Evaluate the Safety, Tolerability, and Pharmacokinetics of Switching from Oral Risperidone to Risperidone Implant (DLP-114)” (Final Protocol Amendment DLP-114-03 Revision E, 12 July 2021). Mock shells will be produced as a separate working document to facilitate programming of Tables, Figures, and Listings (TFLs) according to the SAP. The SAP is to be interpreted in conjunction with the protocol, and supersedes the statistical considerations identified in the protocol. If the final clinical study report contains changes to any planned statistical analyses, the justification for any such differences will be fully documented in the clinical study report (CSR).

1.1 Study Objectives

1.1.1 Primary Objective

Evaluate the safety and tolerability of DLP-114:

- Determine the number and percentage of patients experiencing a treatment-emergent adverse event;
- Evaluate the incidence of local site reactions;
- Assess the tolerability of implantation and explantation procedures.

1.1.2 Secondary Objectives

- Measure the plasma concentration of risperidone and 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) following repeated oral administrations.
- Measure the plasma concentration of risperidone and 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) following switch from oral risperidone to subcutaneous implantation of two DLP-114 devices.
- Measure exploratory treatment outcomes using 2 psychiatric rating scales: the Clinical Global Impression (CGI-I) rating scale and the PANSS.
- Measure the amount of risperidone drug substance remaining in the DLP-114 reservoir following its removal, in order to estimate average daily output and duration.
- Determine average depth of device placement and any potential migration.

2 Study Design

The study is an open-label, parallel group design aimed at assessing the safety and tolerability of DLP-114 and evaluating its utility in achieving a PK profile that is comparable to the marketed oral form of risperidone.

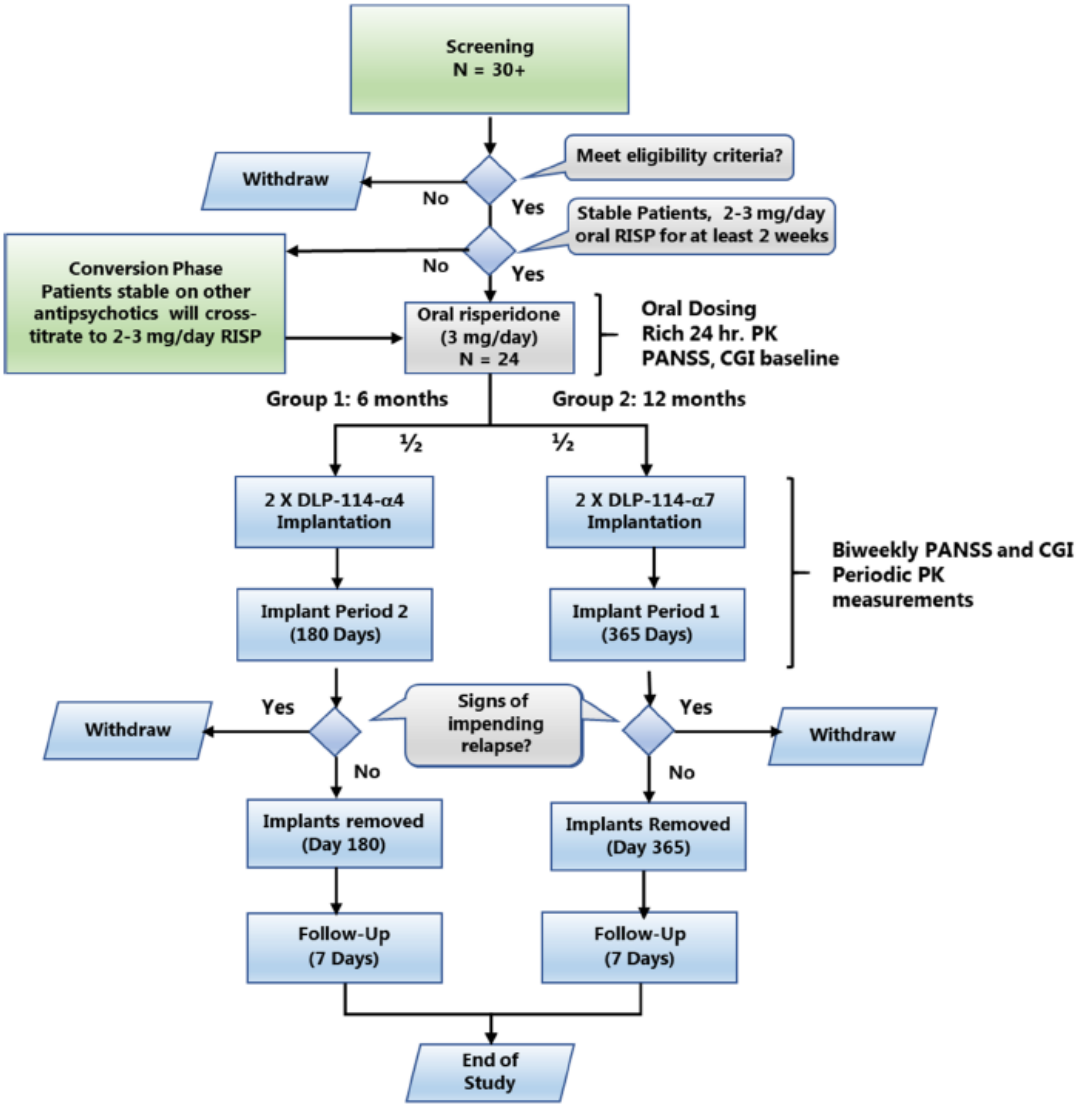
Treatment of each patient will be conducted in four sequential periods (subjects will either enter the conversion phase or the unsupervised oral risperidone [3 mg/day] period) following screening. (**Figure 1**)

1. Conversion phase, if applicable (Cross-titration, at the PI’s discretion, from other

antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks to achieve an oral risperidone dose of 3 mg by Day -14) – oral risperidone (3 mg/day)

2. Unsupervised oral risperidone (3 mg/day)
3. Supervised oral risperidone (3 mg/day)
4. DLP-114 implant treatment with oral supplement (1 day)
5. DLP-114 implant treatment
6. Follow-up

Figure 1: Flowchart of Study Design



2.1 Unsupervised Oral Risperidone Period (Day -7 to -5)

Eligibility in the Study requires that patients have been stable on 2-3 mg/day oral risperidone for a minimum of 2 weeks before implantation. Starting on Day -7, and as early as Day -10 at the PI's discretion, patients who are currently on oral risperidone therapy (2-3 mg/day) will be instructed to take a dose of 3 mg/day oral risperidone (unsupervised), daily through Study Day -5.

2.2 Oral risperidone conversion phase (minimum of 2 weeks prior to implant)

Patients who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) will cross-titrate, at the PI's discretion, from the other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks. The objective of the oral conversion phase is for all subjects to achieve an oral risperidone dose of 3 mg by Day -14.

2.3 Supervised Oral Risperidone Period (Days -4 to 1)

On Days -4, -3 and -2 patients will be required to attend the clinical facility for outpatient visits toreceive a dose of 3 mg/day oral risperidone (under the supervision of the clinical facility staff) and safety assessments.

On the morning of Day -1 patients will be admitted and confined to the clinical facility overnight and for a period of 7 days. Following admission each patient will receive an additional supervised oral dose of risperidone (3 mg). PK samples will be collected pre-dose and at a number of time points following the fourth dose of oral risperidone. On the morning of Day 1 (immediately after the 24-hour PK sample, and immediately before the DLP-114 implantation), another oral dose will be administered (3 mg).

2.4 DLP-114 Implant Treatment Period with Oral Supplement (Days 1 to 2)

Patients will be assigned to Group 1 (DLP-114-α4) or Group 2 (DLP-114-α7). On Day 1, following measurements of vital signs and collection of a pre-implantation blood samples (for PK), each Group 1 patient will be implanted with two DLP-114-α4 and each Group 2 patient with two DLP-114-α7 devices. Following implantation, vital signs will be monitored, an ECG will be administered, and safety laboratory tests will be performed. PK samples will be collected at several time points after DLP-114 implantation. A final oral dose of risperidone (3mg) will be administered 24 hours after implantation.

2.5 DLP-114 Implant Treatment Period (Days 2-183 [± 7] or 2-365 [± 7] for Groups 1 and 2, Respectively)

Patients will remain in the clinical facility for 72 hours post-implantation and will be discharged no later than Day 7. PK samples will be collected each day during the confinement period and on the day of discharge.

Both groups will return to the clinical facility for outpatient visits once every week for safety assessments and PK sampling during the first 4 weeks after implantation (i.e., days 7, 14, 21 and 28) and bi-weekly after that. Safety assessments will include vital signs, measurement of body weight, assessment of AEs, C-SSRS, review of con meds, and inspection of DLP-114 implant site at every visit. Other

safety assessments (performed less frequently) will include a urine drug test, urine pregnancy test (female patients only), safety lab test (blood and urine), ECG, CGI-I, PANSS, BARS, SAS, and AIMS (see Section 2.7, Overall Schedule of Assessments).

An ultrasound will be conducted on day 14 and prior to implant removal in order to assess the depth of the implanted device and any possible vertical migration over time.

Assessments may be performed more frequently than what's stated in the Schedule of Assessments based on the PI's discretion. If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping.

On the morning of Day 183 [± 7 days] (α4 Group 1) or Day 364 [± 7 days] (α7 Group 2) patients will attend the clinical facility for the removal of the DLP-114 implants. Vital signs and body weight will be obtained and a PK sample collected prior to the removal of the implant. Following the removal of the implant, vital signs will be monitored, safety laboratory tests will be conducted and a number of PK samples collected. Patients will be confined to the clinical facility for 2 nights and will be discharged on the following day (Day 185 [± 7 days] for Group 1 or Day 366 [± 7 days] for Group 2) following inspection of the implant site, a complete physical exam, safety review and PK sampling. It may not be practical to schedule the exact explantation date at the time of patient enrollment (i.e., 6-12 months in advance). As a result, the target date of explantation may be adjusted [± 7 days] in order to accommodate potential scheduling conflicts with the physician responsible for the explantation procedure. In the event that the explantation date is adjusted, all the target dates following explantation will also be adjusted accordingly.

2.6 **Follow-up and End of Study Visits (7 days [±1] after device removal)**

Patients will return to the clinical facility 3 days post implant removal (Day 186 for Group 1 and Day 367 for Group 2) for safety assessments and collection of PK samples.

Each patient's participation in this study will conclude on Day 190 (Group 1, α4) or Day 371 Group 2, α7), 7 days post implant removal. Patients will attend the clinical facility for final safety assessments, including vital signs, an abbreviated physical examination, inspection of the implantation site, body weight, and AE assessment/review.

2.7 Schedules of Assessments

2.7.1 Group 1

Treatment Period	Screening	Conversion Phase[1]	Oral Treatment Period (Unsupervised)			Oral Treatment Period (Supervised)				Implant + Oral Period		Implant Treatment Period																		Recovery Period		Follow Up	EOS		ET[24]	ET Oral
Study Day	Varies (28 day window)	Varies to -5	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	14	21	28	42	56	70	84	98	112	126	140	154	168	183	184	185	186	190			
Confinement									X	X	X	X	X	X	X														X	X						
Outpatient Visit	X	X				X	X	X								X	X	X	X	X	X	X	X	X	X	X	X	X	X	¥		X	X	X		X	X
ASSESSMENT																																					
Cross titrate from other antipsychotic to 2-3 mg/day risperidone[1]		X																																			
Informed Consent	X																																				
Review of Eligibility Criteria	X																																				
Demographics	X																																				
Medical History	X																																				
Height	X					X																															
Body Weight	X					X										X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X			
Calculation of BMI	X					X																															
Review of Prior Medications	X					X																															
Physical Examination (Complete)	X																															X				X	
Viral Serology	X																																				
Alcohol Breath Test[4]	X								X																												
Urine Drug Screen[4]	X								X														X							X						
Serum hCG Pregnancy Test[2]	X																																				
Urine hCG Pregnancy Test[2,4]						X			X										X		X		X		X		X			X				X	X	X
Safety Laboratory Tests (blood)[4]	X								X							X			X				X				X			X[11]				X[11]	X[11]	X
Safety Laboratory Tests (urine)[4]	X								X							X			X				X				X			X[11]				X[11]	X	X
12-lead ECG[3,4]	X								X	X[7]	X[8]					X			X				X				X			X[11]				X[11]	X	X
Vital Signs[25]	X	X				X[5]	X	X	X[6]	X[6,8]	X[8]	X[10]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]	X[13]	X[14]	X	X	X[12]	X	X
CYP2D6 Genotype	X																																				
CGI-S	X								X																												
CGI-I[4]																X	X		X		X		X		X		X		X	X					X	
PANSS[4]	X								X														X							X					X	
C-SSRS	X	X				X			X	X						X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
BARS[4]	X								X																				X						X		
SAS[4]	X								X																				X						X		
AIMS[3]	X								X																				X						X		
Self Administration of Investigational Product Under Supervision (Oral)						X	X	X	X	X[19]	X[9]																										
Self Administration of Investigational Product Not Under Supervision (Oral)			X	X	X																																
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Update/Review of Concomitant Medications		X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for PK[15]									X[17,18]	X[19,20]	X[21]	X[22]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]	X[13]	X[14]	X		X[15]	
Implant Device Administration										X																											
Issuing of study card and/or safety alert bracelet																X																					
Implant Site Inspection										X	X[9]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[13]	X[14]	X	X	X	X
Ultrasound[4]																	X													X							
Implant removal																														X					X		

2.7.2 Group 2

Treatment Period	Screening	Conversion Phase[1]	Oral Treatment Period (Unsupervised)			Oral Treatment Period (Supervised)				Implant + Oral Period		Implant Treatment Period			
Study Day	Varies (28 day window)	Varies to -5	-7	-6	-5	-4	-3	-2	-1	1	2	3	4	5	6
Confinement									X	X	X	X	X	X	X
Outpatient Visit	X	X				X	X	X							
Cross titrate from other antipsychotic to 2-3 mg/day risperidone[1]		X													
Informed Consent	X														
Review of Eligibility Criteria	X					X									
Demographics	X														
Medical History	X														
Height	X					X									
Body Weight	X					X									
Calculation of BMI	X					X									
Review of Prior Medications	X					X									
Physical Examination (Complete)	X														
Viral Serology	X														
Alcohol Breath Test[4]	X								X						
Urine Drug Screen[4]	X								X						
Serum hCG Pregnancy Test [2]	X														
Urine hCG Pregnancy Test[2,4]						X			X						
Safety Laboratory Tests (blood)[4]	X								X						
Safety Laboratory Tests (urine)[3]	X								X						
12-lead ECG[3,4]	X								X	X[7]	X[8]				
Vital Signs[25]	X	X				X[6]	X	X	X[6]	X[6,7]	X[9]	X[10]	X	X	X
CYP2D6 Genotype	X														
CGI-S	X								X						
CGI-I[4]															
PANSS[4]	X								X						
C-SSRS	X	X				X			X	X					
BARS[4]	X								X						
SAS[4]	X								X						
AIMS[4]	X								X						
Self Administration of Investigational Product Under Supervision (Oral)						X	X	X	X	X[19]	X[9]				
Self Administration of Investigational Product Not Under Supervision (Oral)			X	X	X										
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Update/Review of Concomitant Medications		X				X	X	X	X	X	X	X	X	X	X
Blood Sampling for PK[16]									X[17,18]	X[19,20]	X[21]	X[22]	X	X	X
Implant Device Administration										X					
Issuing of study card and/or safety alert bracelet															
Implant Site Inspection										X	X[9]	X	X	X	X
Ultrasound[4]															
Implant removal															

Treatment Period	Implant Treatment Period											
Study Day	7	14	21	28	42	56	70	84	98	112	126	140
Confinement												
Outpatient Visit	X	X	X	X	X	X	X	X	X	X	X	X
			ASSESSMENT									
Cross titrate from other antipsychotic to 2-3 mg/day risperidone[1]												
Informed Consent												
Review of Eligibility Criteria												
Demographics												
Medical History												
Height												
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X
Calculation of BMI												
Review of Prior Medications												
Physical Examination (Complete)												
Viral Serology												
Alcohol Breath Test[4]												
Urine Drug Screen[4]								X				
Serum hCG Pregnancy Test [2]												
Urine hCG Pregnancy Test[2,4]				X		X		X		X		X
Safety Laboratory Tests (blood)[4]	X			X				X				X
Safety Laboratory Tests (urine)[3]	X			X				X				X
12-lead ECG[3,4]	X			X				X				X
Vital Signs[25]	X	X	X	X	X	X	X	X	X	X	X	X
CYP2D6 Genotype												
CGI-S												
CGI-I[4]	X	X		X		X		X		X		X
PANSS[4]								X				
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X
BARS[4]												
SAS[4]												
AIMS[4]												
Self Administration of Investigational Product Under Supervision (Oral)												
Self Administration of Investigational Product Not Under Supervision (Oral)												
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X
Update/Review of Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for PK[16]	X	X	X	X	X	X	X	X	X	X	X	X
Implant Device Administration												
Issuing of study card and/or safety alert bracelet	X											
Implant Site Inspection	X	X	X	X	X	X	X	X	X	X	X	X
Ultrasound[4]		X										
Implant removal												

Treatment Period	Implant Treatment Period															
Study Day	154	168	182	196	210	224	238	252	266	280	294	308	322	336	350	364
Confinement																X
Outpatient Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	~~X~~
Cross titrate from other antipsychotic to 2-3 mg/day risperidone[1]																
Informed Consent																
Review of Eligibility Criteria																
Demographics																
Medical History																
Height																
Body Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Calculation of BMI																
Review of Prior Medications																
Physical Examination (Complete)																
Viral Serology																
Alcohol Breath Test[4]																
Urine Drug Screen[4]			X													X
Serum hCG Pregnancy Test [2]																
Urine hCG Pregnancy Test[2,4]			X		X		X		X	X		X		X		X
Safety Laboratory Tests (blood)[4]			X				X			X			X			X[11]
Safety Laboratory Tests (urine)[3]			X				X			X			X			X[10]
12-lead ECG[3,4]			X				X			X			X			X[11]
Vital Signs[25]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[12]
CYP2D6 Genotype																
CGI-S																
CGI-I[4]		X	X		X		X		X	X		X		X	X	X
PANSS[4]			X							X						X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BARS[4]					X		X		X					X	X	
SAS[4]					X		X		X					X	X	
AIMS[4]					X		X		X					X	X	
Self Administration of Investigational Product Under Supervision (Oral)																
Self Administration of Investigational Product Not Under Supervision (Oral)																
Adverse Event Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Update/Review of Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Sampling for PK[16]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[23]
Implant Device Administration																
Issuing of study card and/or safety alert bracelet																
Implant Site Inspection	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ultrasound[4]																X
Implant removal																X

Treatment Period	Recovery Period		Follow Up	EOS		ET[24]	ET Oral
Study Day	365	366	367	371			
Confinement	X						
Outpatient Visit		X	X	X		X	X
Cross titrate from other antipsychotic to 2-3 mg/day risperidone[1]							
Informed Consent							
Review of Eligibility Criteria							
Demographics							
Medical History							
Height							
Body Weight				X			
Calculation of BMI							
Review of Prior Medications							
Physical Examination (Complete)		X				X	
Viral Serology							
Alcohol Breath Test[4]							
Urine Drug Screen[4]							
Serum hCG Pregnancy Test [2]							
Urine hCG Pregnancy Test[2,4]				X		X	X
Safety Laboratory Tests (blood)[4]						X[11]	X[11]
Safety Laboratory Tests (urine)[3]						X[11]	X
12-lead ECG[3,4]						X[10]	X
Vital Signs[25]	X[13]	X[14]	X	X		X[12]	X
CYP2D6 Genotype							
CGI-S							
CGI-I[4]						X	
PANSS[4]						X	
C-SSRS		X	X	X		X	
BARS[4]						X	
SAS[4]						X	
AIMS[4]						X	
Self Administration of Investigational Product Under Supervision (Oral)							
Self Administration of Investigational Product Not Under Supervision (Oral)							
Adverse Event Monitoring	X	X	X	X		X	X
Update/Review of Concomitant Medications	X	X	X	X		X	X
Blood Sampling for PK[16]	X[13]	X[14]	X			X[18]	
Implant Device Administration							
Issuing of study card and/or safety alert bracelet							
Implant Site Inspection	X[13]	X[14]	X	X		X	
Ultrasound[4]							
Implant removal						X	

Footnotes: Overall Schedule of Assessments (6-Month Arm and 12-Month Arm)

[1] Patients who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) will have weekly visits during the conversion phase, during which they will cross-titrate, at the PI's discretion, from the other antipsychotic(s) to oral risperidone therapy over a minimum of 2 weeks. The objective of the oral conversion phase is for all subjects to achieve an oral risperidone dose of 3 mg by Day -14.
[2] Females only
[3] All ECGs should be obtained prior to vital signs and blood sampling when applicable.
[4] May be performed more frequently based on symptoms at the PI's discretion
[5] Pre-dose
[6] Pre-implantation
[7] 4 hours post-implantation
[8] Every hour for the first 8 hours post-implantation
[9] Approximately 24 hours post-implantation
[10] Approximately 48 hours post-implantation
[11] 4 hours following removal of the DLP-114 implant
[12] Every hour for the first 4 hours following removal of the DLP-114 implant
[13] 24 hours following removal of the DLP-114 implant
[14] 48 hours following removal of the DLP-114 implant
[15] Prior to removal
[16] See Appendix 2 of the protocol. Pharmacokinetic sample collection schedule
[17] Within 10 min prior to dose administration
[18] 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours post-dose
[19] 1 hour (± 30 min) prior to DLP-114 implantation
[20] 1, 2, 3, 4, 6, 8 and 12 hours post-implantation
[21] 24, 28, 32 and 36 hours following implantation of DLP-114
[22] 48 and 52 hours following implantation of DLP-114
[23] 1, 2, 3, 4, 6, 8- and 12-hours following removal of the DLP-114 implant
[24] Patients will be requested to return to the clinic for a follow up visit 6 (±3) days followingthe removal of the implant, for implant site inspection and AE assessment.
[25] Vital signs will include systolic and diastolic blood pressure, pulse, body temperature, andrespiratory rate. In addition, orthostatic blood pressure and pulse will be collected after 1, 3, and 5 minutes standing at Screening, on Day 1 prior to the implant and 4 hours post-implantation, and on Day 3 approximately 48 hours post-implantation.

2.8 Number of Patients

Two groups of 12-15 schizophrenia patients (12-15 Group 1 and 12-15 Group 2) who have been stable on 2-3 mg/day oral risperidone for at least 2 weeks, or who are stable on an antipsychotic other than oral risperidone (2-3 mg/day) but complete the conversion phase, will receive the DLP-114 implants. Group 1 will receive 2 DLP-114-α4 devices and Group 2 will receive 2 DLP-114-α7 devices.

2.9 Sample Size Determination

The maximum sample size is 30. The primary objective of this study is to determine safety and tolerability of DLP-114 and as such the sample size for this study was based upon qualitative considerations. No formal sample size calculations were performed.

2.10 Randomization

Each patient will be assigned a unique identification number upon screening. Patients who complete the study screening assessments and meet all the eligibility criteria will be assigned a unique randomization identification number at the time of the first dosing, different from the screening number, and will receive the corresponding product, according to a pre-specified randomization scheme.

Patients will be assigned to one of two groups that will be dosed in parallel. The dosing period for Group 1 is 183 (± 7) days and Group 2 364 (± 7) days. The study is open label.

2.11 Study Endpoints

2.11.1 Safety Endpoints

Safety endpoint evaluations include the following:

- Incidence and severity of AEs
- Local tolerance at the implantation site will be examined and scored for severity of visible signs of irritation/inflammation
- Tolerability of the implantation and explantation procedures
- Vital signs parameters
- Physical examination findings
- Electrocardiogram parameters
- Safety laboratory test parameters (serum chemistry, hematology, urinalysis)
- C-SSRS
- EPS Assessments (BARS, SAS, AIMS)

2.11.2 Pharmacokinetic Endpoints

Evaluation of plasma concentrations of risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone).

PK parameters to be calculated for oral risperidone treatment period include:

- Maximum concentration (C_{max})
- Minimum concentration (C_{min})
- Time to maximum concentration (T_{max})
- Time to minimum concentration (T_{min})
- Terminal half-life ($t_{1/2}$)

PK parameters to be calculated for implant treatment period include:

- Maximum concentration (C_{max})
- Minimum concentration (C_{min})
- Time to maximum concentration (T_{max})
- Time to minimum concentration (T_{min})
- Average concentration (C_{ave})

2.11.3 Exploratory Treatment Outcomes

Exploratory treatment outcomes will be assessed using 2 psychiatric rating scales: the Clinical Global Impression (CGI) rating scale and the PANSS.

2.11.4 Device Endpoints

- Implant spontaneous migration away from the initial subcutaneous implantation areaduring the implant treatment period.
- Amount of unreleased drug substance remaining in the DLP-114 implant following its removal.
- Depth of device placement

2.11.5 Duration of the Study

2.11.5.1 Group 1

The study duration for each Group 1 patient will be up to 236 days (up to 278 with the conversion phase, if applicable). This includes the following:

- Screening period (28 days)
- Conversion phase (minimum 2 weeks)
- Oral risperidone (3 mg/day, 3-6 days, unsupervised)
- Oral risperidone (3 mg/day, 4 days, supervised)
- DLP-114 α4 implant treatment (Group 1 183 days [± 7] days)
- Follow-up (7 (± 1) days)

2.11.5.2 Group 2

The study duration for each Group 2 patient will be up to 417 days (up to 459 with the conversion phase, if applicable). This includes the following:

- Screening period (28 days)

- Conversion phase (minimum 2 weeks)
- Oral risperidone (3 mg/day, 3-6 days, unsupervised)
- Oral risperidone (3 mg/day, 4 days, supervised)
- DLP-114 α7 implant treatment (364 [± 7] days)
- Follow-up (7 (± 1) days)

If patients experience any clinically significant adverse events during the study, they may be required to remain in the clinical facility for further observation at the discretion of the investigator. If a serious adverse event is observed the active moiety concentration will be measured to evaluate the possibility of dose-dumping.

2.12 **Study Data**

The study data to be analyzed include all clinical data captured by the case report form (CRF), including safety lab data. The CRF database will be locked for the final analyses.

3 GENERAL ANALYSIS DEFINITIONS

All analysis dataset preparations and statistical analyses will be performed using SAS® version 9.4 or higher. No imputation will be performed for missing data. Listings for CSR Appendix 16.2 will include all the patient data points being collected or derived for analyses. Data listings will be provided for all patients up to the point of withdrawal.

3.1 **Treatment Groups**

The analyses will be conducted by treatment group (DLP-114- α4 and DLP-114- α7).

3.2 **Statistical Hypothesis Tests**

No statistical hypothesis tests will be performed for the analyses described in this SAP.

3.3 **Reference Date, Baseline, and Repeat/Unscheduled Assessments**

A reference date refers to the start of the study drug administration for each treatment period. All assessments at all visits will be assigned a day relative to this date within each treatment period. The relative day will be defined as: visit date – reference date + 1 for visits on or after the reference date and visit date – reference date for visits before the reference date. Consequently, there is no ‘Day 0’ defined.

In general, the baseline is defined as the last evaluation prior to device implantation on Day 1.

Repeat/unscheduled assessments will not be used in descriptive statistics or any per-time point analysis but will be shown in listings as applicable. Pre-dose unscheduled assessments will be taken into account for baseline determination and post first dose unscheduled assessments will be taken into account for worst-case determination as applicable.

3.4 **Analysis Populations**

3.4.1 Pharmacokinetic Population

The pharmacokinetic population will be defined in a separate document.

3.4.2 Safety Population

All patients who received at least one dose of the study drug via the DLP-114 implant device will be included in the safety analysis.

3.5 **Patient Replacement**

Final confirmation of eligibility will be checked on dosing day. Patients who withdraw consent from the study prior to completion of the supervised oral risperidone treatment period may be replaced at the discretion of the investigator and following consultation with the sponsor.

Patients who withdraw consent from the study prior to completion of the first week of the implant treatment period for reasons other than occurrence of an SAE will be replaced.

3.6 **Descriptive Summaries**

Summary statistics and statistical analyses will generally only be performed for patients included in the relevant safety and pharmacokinetic populations. For the calculation of summary statistics and statistical analysis, unrounded data will be used. All tabulated summaries will include two treatment periods (oral treatment period prior to implant of the device and implant treatment period, including the oral plus implant period) and applicable treatment groups within each treatment period. For endpoints that are continuous in nature: number of observations, mean, median, minimum, maximum, and standard deviation (SD) will be presented as descriptive summary. For endpoints that are categorical in nature: frequency counts and percentages will be presented as descriptive summary.

The number of decimal places to display for calculated data will be determined by the original scale of the data. Means and medians will be reported with one (1) additional decimal place. Standard deviation will be reported with two (2) additional decimal places. Minimum and maximum will be reported with the same number of significant digits as the method of capture.

4 PLANNED INTERIM ANALYSIS

An administrative interim analysis may be conducted for this open-label study when Group 1 (DLP-114-α4) has completed the study and when data from Group 2 (DLP-114-α7) is has been collected up to 6 months. The study will not be stopped or modified as a result of this interim analysis. Deliverables will compare finalized Group 1 data against data in group 2 up to 6 months post-implant, day 183 of the study. Deliverables may include tables and listings associated with adverse events and serious adverse events, extrapyramidal symptoms (captured in the AIMS, BARS, and SAS questionnaires), ECG data, and suicidal ideation symptoms (captured by C-SSRS questionnaire). Device safety deliverables related to the implant may include any adverse events occurring during the device implant procedure, local irritation near the implant site, and device migration over the study duration. Efficacy deliverables may include descriptive statistics for PANSS and CGI questionnaires that measure relevant mental illness symptoms. PK analysis for this interim analysis may be described in a separate document. No hypothesis testing will be produced at this time.

5 PATIENT INFORMATION

In general, all patient-level parameters will be summarized for the Safety Population based on randomized treatment groups, unless stated otherwise.

5.1 Disposition Information

Summaries will be provided for the following disposition information: number of patients screened, screening failures, randomized, completed treatment, and completed or discontinued study with the reasons of discontinuation. The reasons of discontinuations include following categories:

- Patient voluntarily withdrew from the study
- Patient entered another drug study involving an investigational drug
- Patient non-compliant
- Patient lost to follow-up
- Adverse event or complication
- Other medical reason
- Patient died
- Signs of impending relapse
- Other

5.2 Protocol Deviations

All reported major protocol deviations and determined exclusions from any analysis population(s) will be documented and included in the CSR.

5.3 Demographics and Baseline Characteristics

Descriptive statistics or frequency tabulation will be provided for the following parameters.

5.3.1 Demographic Parameters at Baseline

- Age (years)
- Sex (Male, Female)
- Race (White, Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Weight at baseline (kg)
- Height at baseline (cm)
- Body Mass Index (BMI) = Weight (kg) / [Height (m)]^2 rounded to 1 decimal.

5.4 Medical History

All reported medical history will be coded by Medical Dictionary for Regulatory Activities (MedDRA, version 23.1), and summarized by MedDRA system organ class and preferred term, in order of descending overall frequency for the Safety Population.

5.5 Prior and Concomitant Medications

All reported medications will be coded using the World Health Organization-Drug Dictionary (WHODrug version B3, September 2020) and summarized separated for each of following two categories:

1) Prior medication: medication received during the 45 days prior to Screening but is no longer being taken, collected on the CRF page “Concomitant/Prior Medication.”
2) Concomitant medication: medication received between Screening and the end of the study, collected on the CRF page “Concomitant/Prior Medication.”

Prior medications will be included in the patient data listing. A frequency tabulation for concomitant medications will be shown by WHO-DD ATC class level 4 and preferred term for the Safety Population.

5.6 Study Drug Administration

Study drug and device administration, including dose, will be summarized and listed by patient for each treatment.

6 PHARMACOKINETICS

Methodology for calculation of PK parameters for risperidone, 9-OH risperidone and active moiety (risperidone + 9 OH risperidone) and specifications for analysis will be provided in a separate document.

7 SAFETY

All safety analyses will be done on the Safety Population.

All safety parameters will be summarized based on the actual treatment group within each treatment period.

7.1 Adverse Events

7.1.1 Coding of Adverse Events

The verbatim terms of adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1). Events are summarized by system organ class and preferred term.

7.1.2 Treatment-Emergent AEs

Pre-treatment AEs are defined as AEs that were reported or worsened after signing the informed consent form up to the start of first study drug dosing, including prior to oral risperidone. Pre-treatment AEs will be listed, only. Treatment-emergent AEs (TEAE) are defined as AEs that were reported or worsened on or after the start of device implantation. Adverse events emerging during the oral risperidone treatment period (supervised and unsupervised, combined) will also be reported separately.

7.1.3 Variables Attributed to Adverse Events:

- AE term (verbatim and MedDRA preferred term and system organ class)
- Start date and time, End date and time, and duration of AE
- Serious AE (Yes/No), if yes classification will be listed
- Severity (Mild, Moderate, Severe, Life-Threatening, Death)

- Relation to study treatment (Unrelated, Unlikely Related, Possibly Related, Probably Related, Definitely Related)
- Action taken (No Action, Medication Required, Tests Required, Hospitalization Required (or Prolonged), Investigational Product Administration Interrupted/Withdrawn, Other)
- Outcome of AE (Recovered, Recovering, Recovered with Sequelae, Not Recovered, Fatal, Unknown)

7.1.4 Analysis Methods

There will be no formal statistical testing.

A summary will be provided for the following TEAEs for each treatment including the numbers of patients and percentages for the following:

- any TEAE
- any TEAE at least possibly related to study medication (related)
- any TEAE by severity
- any serious TEAE
- any TEAE leading to early withdrawal
- any TEAE leading to death

The adverse events will be shown by MedDRA system organ class and preferred term, in order of descending overall frequency. For each TEAE, the percentage of patients who experience at least 1 occurrence of the given event will be summarized for each treatment. Incidence tabulations will be provided for overall summary, summary by highest severity, and summary by relatedness.

Oral risperidone adverse events will be summarized similarly.

7.2 **Clinical Laboratory Evaluations**

Clinical laboratory findings will be summarized by type of test, described below.

Hematology: Leukocytes, erythrocytes, hemoglobin, hematocrit, thrombocytes; (partial automated differentiation): lymphocytes, monocytes, eosinophils, basophils, neutrophils.

Serum Chemistry: Sodium, potassium, calcium, phosphate, blood urea nitrogen (BUN), serum creatinine, glucose, lactic acid dehydrogenase (LDH), alanine transferase (ALT), aspartate transferase (AST), total bilirubin, alkaline phosphatase, gamma glutamyl transferase (GGT), total proteins, albumin and urates.

Lipid profile analysis: total cholesterol, LDL, HDL, non-HDL and triglycerides.

Coagulation: Prothrombin time (PT), international normalized ratio (INR) and activated partial thromboplastin time (aPTT).

Urinalysis: Urine samples for urinalysis will be collected at specified time points. The following urinalysis parameters will be assessed: hemoglobin, urobilinogen, ketones, bilirubin, glucose, protein, nitrite, leukocytes, pH, specific gravity.

Normal reference ranges and markedly abnormal results will be used in the summary of laboratory data. Raw data and change from baseline in clinical laboratory parameters will be summarized using descriptive statistics. Abnormalities in clinical laboratory measures will be based on pre-defined normal ranges and will be tabulated by study

treatment showing patient counts and percentages. A listing of patients with any laboratory results outside the reference ranges that are deemed clinically significant will be provided.

7.3 Vital Signs

Summary statistics will be presented for the observed values and change from baseline values (as appropriate) for each treatment at each collected time point for all vital signs measured: Oral Temperature (Celsius), Heart Rate (beats/min), Systolic Blood Pressure (mmHg), Diastolic Blood Pressure (mmHg), Respiratory Rate (breaths/min). Abnormalities vital signs will be based on pre-defined normal ranges and will be tabulated by study treatment showing patient counts and percentages. Summaries and individual patient listings will be provided for both resting and orthostatic vital signs. Orthostatic vital signs are defined by the change from sitting to standing at 1 minute, 3 minutes and 5 minutes for heart rate and blood pressure.

7.4 Electrocardiogram

P-R interval (msec), QT interval (msec), QRS duration (msec), QTcF intervals (msec) using Fridericia's correction formula, R-R intervals (msec), and ventricular heart rate (beats/min) will be collected on CRF. Actual values and changes from baseline will be summarized at each scheduled timepoint for each treatment. In addition, frequency tabulation of the overall ECG results (Normal, Abnormal NCS, and Abnormal CS) will be provided.

7.5 Physical Examinations

For physical examination data, when calculating the percentage reporting each category, the “Not Done” category will not be included in the denominator.

The number (N and %) of patients with abnormal physical examinations will be tabulated at each timepoint for each treatment.

7.6 Implantation Site Inspection

Dermal response (Likert scale from 0 = no evidence of irritation to 7 = strong reaction spreading beyond test site) will be summarized at each planned time point using descriptive statistics. Other effects (slight glazed appearance, marked glazing, etc.) will be summarized using frequencies and percentages. For patients with an implant/device event (expulsion, migration), frequencies and percentages will be presented. All implantation site inspection and event data will be provided in listings, including information regarding re-implantation of the device for patients who experienced device expulsion.

7.7 Ultrasound

Depth of device placement at Day 14 and at the visit prior to implant removal will be summarized using descriptive statistics.

7.8 Amount of Unreleased Drug Following Device Removal

The volume of risperidone (ml) remaining in the reservoir following device removal will be summarized descriptively and provided in a listing.

7.9 **C-SSRS**

The Columbia Suicide Severity Rating Scale (C-SSRS, Oquendo et al.) is a suicidal ideation rating scale. The scale identifies behaviors and thoughts that are associated with an increased risk of suicidal actions in the future. The C-SSRS Baseline/Screening version will be conducted at Screening and the Since Last Visit version will be used for all subsequent visits per the Schedule of Events.

The C-SSRS data will be summarized descriptively. Individual patient data will be provided in a listing. Only the following specific suicidal ideation and behavior category questions with any "Yes" responses will be summarized in a frequency distribution table at each post-randomization visit:

- Any Suicidal Ideation Category:
    - Wish to be Dead
    - Non-Specific Active Suicidal Thoughts
    - Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act
    - Active Suicidal Ideation with Some Intent to Act, without Specific Plan
    - Active Suicidal Ideation with Specific Plan and Intent
- Any Suicidal Behavior Category:
    - Completed Suicide
    - Non-Fatal Suicide Attempt
    - Interrupted Attempt
    - Aborted Attempt
    - Preparatory Acts or Behavior
    - Any Suicidal Ideation or Behavior Category

7.10 **Extrapyramidal Symptoms**

7.10.1 Barnes Akasthisia Rating Scale (BARS)

The Barnes Akasthisia Rating Scale (BARS) is a rating scale administered by physicians to assess the severity of drug-induced akathisia. This scale includes objective and subjective items such as the level of restlessness and global clinical assessment of akathisia. The objective and subjective items are rated on a 4-point scale from 0 to 3 and are summed yielding a total score ranging from 0 to 9. The global clinical assessment of akathisia uses a 5-point scale ranging from 0 to 4.

The two sets of scores will be summarized using descriptive statistics; individual item scores and total scores will be provided in a listing.

7.10.2 Abnormal Involuntary Movements Scale (AIMS)

The Abnormal Involuntary Movement Scale (AIMS) is a clinician-administered scale used to detect tardive dyskinesia (TD) and to follow the severity of a person's TD over time. This 12-item anchored scale is clinician administered and scored.

Items 1 through 10 are rated on a 5-point anchored scale:

0=None

1=Minimal, may be extreme normal

2=Mild

3=Moderate

4-Severe

Items 1 through 4 assess orofacial movements.

Items 5 through 7 assess extremity and truncal dyskinesia.

Items 8 through 10 assess global severity as judged by the examiner and the person's awareness of the movements and the distress associated with them.

Items 11 and 12 are yes-no questions concerning problems with teeth and/or dentures, because such problems can lead to a mistaken diagnosis of dyskinesia.

Individual item scores will be summarized using descriptive statistics and individual scores will be provided in a listing.

7.10.3 Simpson-Angus Scale (SAS)
The Simpson-Angus Scale (SAS) is a clinician-administered 10-item rating scale assessing the presence of drug-related extrapyramidal signs. The 10 performance tasks are rated on a scale of 0 – 4 (normal to severe, as relevant to the task assessed). The SAS score is the sum of the 10 performance tasks, ranging from 0 to 40.

Total scores will be summarized using descriptive statistics; individual item scores and total scores will be provided in a listing.

7.11 **Drug, Alcohol, HIV, Hepatitis B & C, CYP2D6 and Pregnancy Screen**

Drug, alcohol, HIV, Hepatitis B & C, CYP2D6 and pregnancy screen data will be included in the patient data listing.

7.12 **Signs of Impending Relapse**

Impending relapse assessment data will be summarized by the number of subjects with at least one sign impending relapse and the percentage for each relapse sign, for each visit and treatment group.

8 EXPLORATORY ANALYSES

8.1 **Clinical Global Impression**

Clinical Global Impression of Severity (CGI-S) will be rated based upon the severity of schizophrenia symptoms at screening and Day -1 during the oral treatment period, immediately prior to the implant + oral period.

Severity of illness will be assessed based on following ratings:

0 = Not assessed

1 = Normal, not at all symptomatic

2 = Minimally symptomatic

3 = Mildly symptomatic

4 = Moderately symptomatic

5 = Markedly symptomatic

6 = Severely symptomatic

7 = Among the most extremely symptomatic subjects

Drug response on symptoms of schizophrenia will be evaluated by the Clinical Global Impressions – Improvement (CGI-I). The CGI-I will be performed according to the timepoints in the Schedule of Assessments. The CGI-I scores range from 1 to 7:

0 = not assessed (missing)

1 = very much improved

2 = much improved

3 = minimally improved

4 = no change

5 = minimally worse

6 = much worse

7 = very much worse

Total scores on the CGI-S and CGI-I will be summarized using descriptive statistics and provided in a listing.

8.1.1 PANSS

The Positive and Negative Syndrome Scale (PANSS) measures positive and negative syndromes associated with schizophrenia. The scale consists of 33 items, 30 of which contribute to the PANSS Total Score (i.e., the sum of the seven P, or positive, items with the seven N, or negative, items with the 16 G, or general pathology, items). The PANSS Total Score ranges from 30 – 210, with higher scores indicating greater pathology.

Individual PANSS items are scored from 1 – 7, as follows:

1 = Absent

2 = Minimal

3 = Mild

4 = Moderate

5 = Moderate/Severe

6 = Severe

7 = Extreme

Total scores on the PANSS will be summarized at planned time points using descriptive statistics; individual item scores and total scores will be provided in a listing. The subsets of Positive (P), Negative (N) and General Pathology (G) will be provided as separate listings.

9 CHANGES FROM PROTOCOL

None

10 REFERENCES

Oquendo MA, Halberstam B, Mann JJ. Colombia Suicide Severity Rating Scale (C-SSRS)– Risk Factors for Suicidal Behavior: The Utility and Limitations of Research Instruments, in Standardized Evaluation in Clinical Practice. First MB, editor. American Psychiatric Publishing; Washington, DC: 2003: 103-131.

11 TABLES, LISTINGS, AND FIGURES

A separate document containing the list of tables, listings, and figures (TFLs) to be included in the post-text Appendix 14 of the CSR will be provided. TFLs may be modified with Sponsor's approval and as deemed necessary without update to the SAP.