1. TITLE PAGE

STATISTICAL ANALYSIS PLAN (SAP)

An Analysis of Efficacy Study of PDC-1421 Treatment in Adult Patients with Attention-Deficit Hyperactivity Disorder (ADHD), Part II

Protocol No.: BLI-1008-002

First subject first visit: April 7, 2022

Last visit of the study: December 6, 2023

Sponsor: BioLite, Inc.
American BriVision Corporation

CRO: BioLite, Inc.

Final Version

Date of issue: April 25, 2024

2. TABLE OF CONTENTS

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADHD	Attention-Deficit/Hyperactivity Disorder
ADHD-RS-IV	Attention-Deficit/Hyperactivity Disorder Rating Scale-IV
AE	Adverse event
BMI	Body Mass Index
CAARS-S:S	Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version
CGI-I	Clinical Global Impression- Improvement
CGI-S	Clinical Global Impression- Severity
CRO	Contract Research Organization
CS	Clinical Significance
C-SSRS	Columbia-Suicide Severity Rating Scale
DSM-5	The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ECG	The Electrocardiogram (ECG) is a graphical recording of the cardiac cycle produced by an electrocardiograph
E-SCT	Empirical-Sluggish Cognitive Tempo
HI	Hyperactivity-impulsivity
IQR	Interquartile Range
IA	Inattention
ITT	Intention-to-treat
LOCF	Last Observation Carried Forward
NCS	Non-Clinical Significance
PE	Physical Examination
PP	Per-protocol
PTAE	Pre-Treatment AE
SAEs	Serious Adverse Event(s).
SD	Standard Deviation
TEAE	Treatment AE

4. PROTOCOL AMENDMENTS

The version of approval protocol after enrolling the first subject was described as follow:

Approved date / Approved by	Final (version:<protocol version>)	Amendment 01 (version:<protocol version>)
USFDA	2022/03/14 (Version 1.6)	2022/11/04 (Version 1.7)
TFDA	2022/04/18 (Version 1.6)	2022/11/09 (Version 1.7)
UCSF	2023/05/22 (Version 1.7	
CGMH	2022/02/18 (Version 1.6)	2022/10/03 (Version 1.7)
CGHG	2022/04/18 (Version 1.6)	2022/10/28 (Version 1.7)
NTUH	2022/02/24 (Version 1.6)	2022/10/28 (Version 1.7)
TVGH	2022/04/12 (Version 1.6)	2022/11/03 (Version 1.7)

This protocol amendment about the statistical analysis is consisted of the following (compared to the final approved protocol)

Page	Version 1.6	Page	Version 1.7
37	None	39	****If the interval of visit 1 and visit 2 is within 7 days, Hematology and Blood chemistry test of visit 2 can be skipped.**
38	None	40	**Drug compliance is important for the safety and efficacy evaluations. Study coordinator needs to make sure drug adherence of the subjects is at least 80% during the treatment period. Otherwise, study coordinator(s) must report a protocol deviation including lower than 80% compliance and over 100% compliance during the treatment period.**
44	**Analyzing of Safety Parameters** The data obtained before study drug administration in Visit 2 are set as baseline.	46	**Analyzing of Safety Parameters** The data obtained before study drug administration **in Visit 2 or Visit 1 (if no data at Visit 2)** are set as baseline.
44	The information of AEs contains characteristic, onset and duration,	46	The information of AEs contains characteristic, onset and duration, the

Page	Version 1.6	Page	Version 1.7
	frequency, the Investigator's opinion of the relationship to the study drug (unrelated, unlikely, possibly, probably, definitely), outcome (recovered, recovered with residual effects, continuing, death, lost to follow-up) and severity.		Investigator's opinion of the relationship to the study drug (unrelated, unlikely, possibly, probably, definitely), outcome (recovered, recovered with residual effects, continuing, death, lost to follow-up), **therapy (no action, treatment given, withdrawn from study, temporarily discontinued)** and severity.

5. INVESTIGATIONAL PLAN

5.1 Objective

5.1.1 Primary objective

The primary objective is to determine the effective doses and treatment period of PDC-1421 Capsule in subject with ADHD Rating Scale-IV (ADHD-RS-IV).

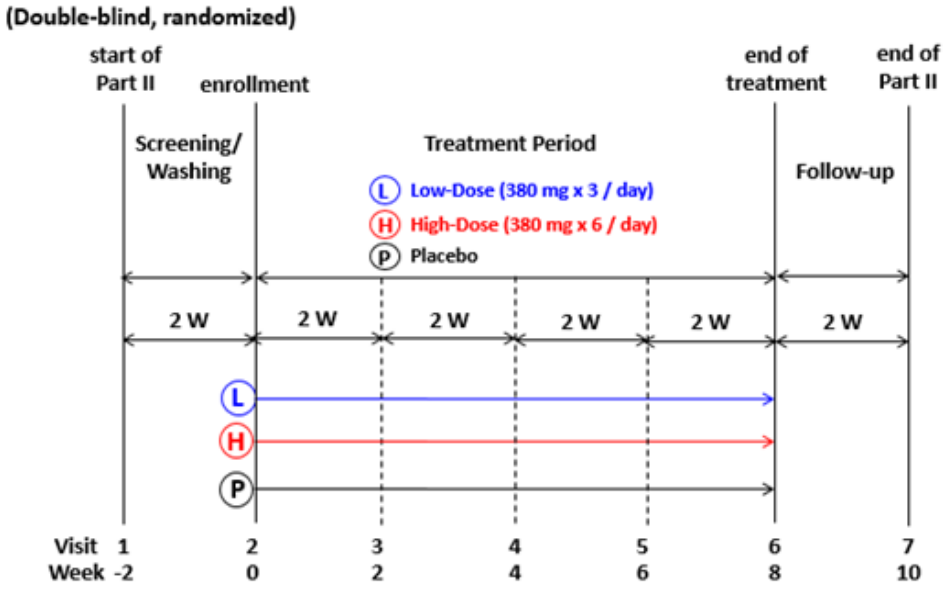
5.1.2 Secondary objective

The secondary objective is to determine the efficacy and safety profile of PDC-1421 Capsule in ADHD with ADHD-RS-IV, CAARS-S:S, E-SCT and CGI-I.

5.2 Study Design

This study is a double-blind, randomized, placebo-controlled, parallel-group study in patients with ADHD according to the Diagnosis and Statistical Manual of Mental Disorders, 5th Edition. At first stage, a number of 69 subjects will be randomly assigned on a 1:1:1 basis to one of the three arms (1 PDC-1421 Capsule plus 1 placebo TID, 2 PDC-1421 Capsules TID, 2 placebo TID) for 8 weeks and evaluated the safety and efficacy every two weeks during the treatment period. An interim analysis will be conducted to evaluate the efficacy of PDC-1421 and to decide whether it is necessary enter the second stage of Part II study in which 30 subjects will be randomly assigned on a 1:1:1 basis to one of the three treatment arms and receive the same treatment.

5.2.1 Schematic Diagram of Study



5.2.2 Study Medication Administration

Subjects will be assigned with a random number to be allocated into 3 treatment groups on a 1:1:1 basis and treated as following dose regimen:

- Placebo: 2 placebo capsules thrice daily after meal for 56 days (8 weeks).
- Low-Dose: 1 placebo capsule and 1 PDC-1421 Capsule (380 mg), thrice daily after meal for 56 days (8 weeks).
- High-Dose: 2 PDC-1421 Capsules thrice daily after meal for 56 days (8 weeks).

5.2.3 Flowchart of study procedures

	Screening	Treatment Period					Follow-up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
***Week**	**-2 to 0**	**0**	**2**	**4**	**6**	**8**	**10**
Informed consent	√						
Subject information	√						
Medical history	√						
DSM-5	√						
CAARS-S:S	√	√	√	√	√	√	√
CGI- S	√	√					
CGI- I			√	√	√	√	√
ADHD-RS-IV	√	√	√	√	√	√	V
E-SCT	√	√	√	√	√	√	√
C-SSRS	√	√	√	√	√	√	√
Concomitant medication	√	√	√	√	√	√	√
Physical examination						√	
Vital sign	√	√	√	√	√	√	√
ECG	√					√	
Laboratory examination							
Pregnancy test	√						√
****Hematology**	√	√		√		√	
****Blood chemistry**	√	√		√		√	
Eligibility evaluation	√						
Drug accountability		√	√	√	√	√	
AE/SAE evaluation		√	√	√	√	√	√

*On ±2 days.

** If the interval of visit 1 and visit 2 is within 7 days, Hematology and Blood chemistry test of visit 2 can be skipped.

5.3 Statistical Methods Planned in the Protocol and Determination of Sample Size

5.3.1 Populations for Analysis

The INTENT-TO-TREAT (ITT) POPULATION consists of all randomized subjects who receive at least one dose of study medication and fulfill all inclusion, exclusion criteria and have any post-baseline safety data collected.

The PER-PROTOCOL (PP) POPULATIO is defined as (1) The drug compliance is at least 80% (2) Subjects have completed data to determine the primary endpoint. (3) Subjects cannot have protocol deviation. The protocol deviation will be defined as (1) Inclusion or exclusion criteria not satisfied. (2) Not permitted concomitant medications (3) Wrong randomized treatment prescribed.

5.3.2 Endpoints

Primary efficacy endpoint

Improvement of 40% or greater in ADHD Rating Scale-Investigator Rated (ADHD-RS-IR) from baseline up to 8 weeks treatment.

Secondary efficacy endpoints:

The secondary efficacy endpoints	Scales
Symptom remission in ADHD-RS-IV (up to 8 weeks treatment)	– Symptom remission in ADHD Rating Scale-Investigator Rated (ADHD-RS-IV total score ≤ 18) score
Score change from baseline (up to 8 weeks treatment)	– ADHD Rating Scale-Investigator Rated (ADHD-RS-IV) score – Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version (CAARS-S:S) score – Empirical-Sluggish Cognitive Tempo (E-SCT) score
Score change from baseline (of 2 or lower up to 8 weeks treatment)	– Clinical Global Impression - improvement (CGI -I) score

Safety endpoints:

1. Change from baseline in:
   - vital sign
   - physical examination
   - electrocardiogram (ECG)
   - laboratory tests (hematology and biochemistry)
2. Incidence of Adverse Event (AE)/ Serious Adverse Event (SAE)
3. Suicidal ideation and behavior by Columbia-Suicide Severity Rating Scale (C-SSRS)

5.3.3 Statistical Evaluation

Summary statistics will be provided for all efficacy, safety, and baseline/demographic variables. For categorical variables, frequency tables will be presented, including percentages. For continuous variables, descriptive statistics such as number of available observations, mean, median, standard deviation, minimum, and maximum will be tabulated. Baseline characteristics (gender, age, BMI, race) will be summarized for all ITT subjects.

5.3.4 Determination of Sample Size

A two stage design developed by Jung (2008) with significant level $\alpha = 0.15$ and power $= 80\%$.

$$\text{Effect of PDC} - 1421 : \begin{cases} \text{Non-effective , if Response Rate } \leq 20\% \\ \text{Worth further study, if Response Rate } \geq 40\% \end{cases}$$

Stage I	Numbers of responders	Stage II
High-Dose (2 PDC-1421 Capsules) **(23 subjects)**	$\mathbf{H - P \geq 0}$	**Add 10 subjects** and proceed to stage II
Low-Dose (1 placebo, 1 PDC-1421) **(23 subjects)**	$\mathbf{L - P \geq 0}$	**Add 10 subjects** and proceed to stage II
Placebo (2 placebo capsules) **(23 subjects)**		**Add 10 subjects** and proceed to stage II

If the difference between the accumulated numbers of responders for any PDC-1421 arm and control arm is less than 4, we reject the drug. The minimum sample size required is to recruit 69 subjects, while the maximum sample size is 99.

5.4 Changes in the Conduct of the Study or Planned Analyses

All the statistical analysis will follow protocolized statistical contents. However, due to the interim report results do not meet the requirement of protocol and the study was terminated, the chi-Square test and Wilcoxon signed-rank test between arms will not be performed.

6. STATISTICAL EVALUATIONS

6.1 Reporting Conventions

Descriptive statistics will be presented for continuous and categorical variables. For continuous variables, number of observations (n), mean, standard deviation (SD), median, interquartile range (IQR), range, minimum (min) and maximum (max) will be presented. Frequencies and percentages will be presented for categorical variables. All descriptive statistics will be rounded to 2 decimal places.

6.2 Data Sets Analyzed

Two study populations are intention-to-treat (ITT) population and per-protocol (PP) populations which are defined in section 5.3.1.

The efficacy evaluations will be performed on both of the ITT and PP datasets while the safety evaluations will be performed on the ITT dataset. The primary conclusion will be made for the primary endpoint on the ITT population. Demographic and baseline (Visit 2) characteristics will be performed on the ITT population.

Sample size, mean, 95% confidence interval of mean, median, standard deviation, inter-quartile range, maximum and minimum will be summarized for continuous variables. For categorical variables, the frequency and percentage will be provided.

6.3 Demographics and Other Baseline Characteristics

Demography and baseline characteristics will be listed by treatment group and analyzed between treatments to ensure comparability. Sample size, mean, median, standard deviation, IQR, range, maximum, and minimum will be summarized for continuous variables. For categorical variables, the frequency and percentage will be provided.

6.3.1 Demographic Data

Demographic data will consist of age (year), height (cm), weight (kg), BMI (kg/m^2), gender and race.

$$\text{Age (years)} = integer\ of\ (date\ of\ initial\ visit - date\ of\ birth)/365.25$$

$$\text{BMI}\ (Kg/m^2) = (weight)/(height/100)^2\ \text{, rounds to first decimal place}$$

Demographic variables will be summarized by center and treatment group. Subjects' gender will be tabulated by treatment group.

6.3.2 ADHD History and Medical History

Frequency table of Diagnosis and Statistical Manual of Mental Disorders-V, text revision (DSM-V-TR) will be presented.

Frequency table of subject with medical history and current medical condition will be presented.

General medical history will be presented in incidence table and listed for each subject. Ongoing medical conditions will also be presented.

6.3.1 Concomitant Medications

Frequency table of subjects with pre-treatment and concomitant medications will be presented.

Pre-treatment medications are the medications taken before the first dosing of study drug, while concomitant medications are those taken during the treatment duration (from first dosing date of study drug to the day before exiting from study).

6.4 Baseline Determined

The data obtained before study drug administration in Visit 2 or Visit 1 (if no data at Visit 2) are set as baseline. For all other endpoint measurements, the last non-missing values before the first IP administration will be used as the baseline for the respective endpoints.

6.5 Study Treatment Administration

6.5.1 Treatment Compliance

Subjects' compliance (%) during the treatment period will be tabulated by center, and treatment and calculated according to the following formula:

$$= \frac{\text{Number of study medication actually took during the extent of exposure}}{\text{Number of study medication should be taken during the extent of exposure (\#)}} \times 100$$

= (number of study medication should be taken per day) * (extent of exposure, section 6.5.2)

6.5.2 Extent of Exposure

Extent of exposure (days) = date of last drug taken – date of first drug taken + 1
If the date of first drug taken is not available, the date when the drug was firstly dispensed will be used for calculation.

If the date of last drug taken is not available, the date will be replaced with that of the last drug return, previous drug taken, or previous drug return in order.

6.5.3 Mean Daily Dose

Descriptive statistics of mean daily dose of the test drug will be presented by center, and treatment.

$$Mean\ daily\ dose = \frac{Number\ of\ study\ medication\ taken}{Extent\ of\ exposure\ (section\ 6.5.2)}$$

6.6 Analysis of Efficacy

6.6.1 Primary Efficacy Endpoint

An improvement of 40% or greater response rate from baseline in treatment group is considered effective and worth further study. The endpoint will be analyzed by checking if the difference of counts of responder is larger than 0 between PDC-1421 arm and placebo arm. Missing data caused by premature termination will be utilized the last observation carried forward (LOCF).

The response rate in the ADHD-RS-IV total score is defined as the following formula.

$$Response\ rate = \frac{score_{visit} - score_{baseline}}{score_{baseline}}$$

and the responder is defined as

$$\text{Responder}: \text{response rate} \geq 40\%$$

The descriptive statistics will include the proportion of subjects who achieved at least 40% improvement of the ADHD-RS-IV total score at Visit 6 by treatment group and placebo group. The frequency distribution of pre-treatment and post-treatment will also be tabulate and report in bar graph.

The primary measure of efficacy was the ADHD-RS-IV, consisting of 18 items designed to reflect current symptomatology of ADHD based on DSM-IV-TR criteria. Each item is scored on a 4-point scale ranging from 0 (reflecting no symptoms) to 3 (reflecting sever symptoms) with total scores ranging from 0 to 54, which is calculated by summing up scores of subscales. The 18 items may be grouped into 2 subscales:

- For inattention (IA) subscale raw score: Add the odd-numbered 9 items. Higher score indicate severe inattention symptoms.
- For hyperactivity-impulsivity (HI) subscale raw score: Add the even-numbered 9 items. Higher score indicate severe hyperactivity-impulsivity symptoms.
- To obtain the total raw score: Add the IA and HI subscale raw scores.

Following SAS procedures will be applied for chi-Square test between arms.

```
%macro;
proc freq data = ____;
    table response*treatment/chisq;
    output out = chiqtest chisq;
run;
%mend;
```

When there has a missing value issue, the following LOCF SAS procedures will be applied.

```
%macro;
DTAT locf1;
   LENGTH dtype $15;
    RETAIN retain;
    SET lab;
    BY usubjid visit;

    IF FIRST . visit ^=0 THEN retain = . ;
    IF qsstresc NE . THEN retain = qsstresc;
      IF qsstresc= . THEN DO;
         qsstresclocf = retain;
          dtype = ''LOCF';
    END;
   ELSE qsstresclocf = qsstresc;
RUN;
%mend;
```

6.6.2 Secondary Efficacy Endpoints

- **ADHD-RS-IV**

The scores of ADHD-RS-IV will be assessed by the descriptive statistics.

- **CGI**

The scores of 2 or lower of CGI will be summarized by way of frequency and percentage.

At the screen and baseline visit, clinicians completed the CGI-S and were asked to evaluate the severity of subjects' illness with respect to ADHD symptoms based on the clinician's experience with this particular population. Possible scores ranged from 1 (normal, not ill at all) to 7 (among the most extremely ill subjects). At all subsequent study visits, clinicians used the CGI-I to rate the subjects' total improvement based on comparison with their baseline assessment from 1 (very much improved) to 7 (very much worse).

- **CAARS-S:S**

The T-scores of CAARS-S:S (Conners et al. 1999) will be assessed for each visit change from baseline by the descriptive statistics

Conners' Adult Attention-Deficit/Hyperactivity Disorder Rating Scale-Self Report: Short Version (Conners et al., 1998; CAARS-S:S) consists of 26 items rated from 0 'not at all, never' to 3 'very much, very frequently.' Four subscales each composed of 5 items (A: Inattention/Memory Problems; B:

Hyperactivity/Restlessness; C: Impulsivity/Emotional Lability; and D: Problems with Self-Concept) as well as a 12-item ADHD index can be computed. The raw scores were converted into standard T-scores by Microsoft Execl program which designed according to the Profile form of CAARS QuikScore forms. A T-score is a standard score with a mean of 50 and a standard deviation of 10 in all samples and across all scales. As a general guide, T-scores can be interpreted using the guidelines provided in the table below. The CAARS-S:S was self-assessed by the subjects from Visit 1 to Visit 7.

Interpretive Guidelines for T-Scores and Percentiles

T-Score Range	Percentile Range	Guideline
Above 70	98+	Very much above average
66 to 70	94 - 98	Much above average
61 to 65	86 - 94	Above average
56 to 60	74 - 85	Slightly above average
45 to 55	27 - 73	Average
40 to 44	16 – 26	Slightly below average
35 to 39	6 – 15	Below average
30 to 34	2 – 5	Much below average
Below 30	< 2	Very much below average

Reference: CAARS Adult ADHD Rating Scales Technical Manual

- **E-SCT**

The scores of E-SCT will be assessed for each visit change from baseline by the descriptive statistics

The E-SCT rating scale queries 15 Sluggish Cognitive Tempo symptoms rated from 0 = Never or Rarely, 1 = Sometimes, 2 = Often, 3 = Very Often, grouped into latent factors of daydreaming, working memory problems, and subjective sleepiness/tiredness. The scale was empirically derived from a set of 44 candidate items 17. Sluggish Cognitive Tempo has been shown to be a statistically related but distinct syndrome with respect to ADHD 18. The range for the Total Score is 0-45. Factor scores are computed using this same method. For data analysis, mean item scores will be used to protect against missing data.

6.7 Analysis of Safety

6.7.1 Adverse events (AEs)

The coding system used will be the Medical Dictionary for Regulatory Activities (MedDRA).
Pre-treatment AE is the AE onset before the first dosing of study drug, while treatment-emergent AE is the one onset after the first dosing of study drug. Pre-treatment AE and treatment emergent AE will be analyzed separately.
Frequency table of subjects with pre-treatment AE (PTAE) and treatment emergent AE (TEAE) will be presented by center and treatment.
For TEAE, adverse event incidents will also be summarized descriptively by system organ class and preferred term using MedDRA. If more than one type of event occurred within a system organ class/ preferred term for the

subject, the subject is counted only once for each system organ class/ preferred term.

For TEAE, incidence tables of severity, action taken, relationship to study drug, outcome and serious AE or not will be presented by center, preferred term and treatment.

The frequency distribution of severity, action taken, relationship to study drug, and outcome of all AE events will be presented by center, and treatment.

6.7.2 Serious adverse events (SAEs)

Incidence of serious adverse event will be tabulated. Serious adverse events incidents will be summarized descriptively by center, system organ class/ preferred term, and treatment group.

6.7.3 Laboratory data

Descriptive statistics of original data and net changes in hematology and biochemistry data will be presented by center, visit, and treatment.

Results of clinical significance with regard to laboratory data will be summarized with frequency and percentage.

6.7.4 Physical Examination (PE)

Incidence table including umber and percentage of patient with abnormal PE will be tabulated by center, visit, and treatment for each body system.

The corresponding body system will be analyzed and reported using a transition table. The type of transition includes no change, change to normal, change to non-clinical significance, (NCS), change to clinical significance (CS) for each body system from baseline (Visit 2).

6.7.5 Vital Signs

Descriptive statistics of net changes in vital signs including systolic and diastolic blood pressure, heart rate and body temperature will be presented by center, visit, and treatment.

Results of clinical significance with regard to vital sign will be summarized with frequency and percentage.

6.7.6 ECG

Frequency table and change in ECG result will be summarized by center, visit and treatment. The transition of ECG is define as following 4 groups: no change, change to normal, change to non-clinical significance, (NCS), change to clinical significance (CS).

6.7.7 C-SSRS (Nilsson et al. 2013)

Results of C-SSRS will be presented by center, visit, and treatment. The baseline of C-SSRS was set at screening visit (Visit 1).

The analysis for C-SSRS will follow the official guidance "Columbia-Suicide Severity Rating Scale - Scoring and Data Analysis Guide." The 10 categories will be defined according to 10 binary responses (yes/no) on the C-SSRS.

Suicidal ideation is identified if the total score of the five suicidal ideation questions (Categories 1-5)>0.
Suicidal behavior is identified if the total score of the five suicidal behavior questions (Categories 6-10)>0.
Suicidal ideation or behavior is identified if the total score of the ten suicidal ideation and behavior questions (Categories 1-10)>0.

Changes of suicidal ideation, suicidal behavior, and suicidal ideation or behavior from baseline during treatment will be summarized in a shift-table by visit, center and treatment.

6.8 Statistical / Analytical Issues

6.8.1 Handling of Dropouts or Missing Data

The data are analyzed utilizing the last observation carried forward (LOCF) technique to impute the missing data.

6.8.2 Multiple Comparisons / Multiplicity

No multiple comparison will be applied in performing statistical analysis.

7. DATA HANDLING PROCEDURE

7.1 Data Storage and Analysis

All data are stored in the VCRO EDC Lite system.

Statistical evaluation will be performed using SAS 9.4 (SAS-Institute Inc.) and Microsoft 365 Excel 2402.

8. APPENDICES

8.1 Table of Contents (TOC) for Tables, Figures and Listing

Refer to section 14 and 16.2 in clinical study report.

No further SAP amendment will be required for the deviation of TOC when the changes are still complied with the main text SAP.

8.2 Version Control Information of SAP

Document	Version	Approved date
Final	20240425_00	April 25, 2024

9. SIGNATURE PAGE

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