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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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Statistical Analysis Plan

ZYN® Patterns of Use Study

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Status: Approved
Date: 6 June 2018
Prepared by: (b) (4)

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Swedish Match North America, its parent and affiliate companies

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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Swedish Match North America, Inc.



Statistical Analysis Plan

ZYN® Patterns of Use Study

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SIGNATURE PAGE

I agree to the terms of this ZYN® Patterns of Use SAP.

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Date: 08 June 2018

(Day Month Year)

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1. LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviations	Definition
AZ	Arizona
CA	California
CO	Colorado
CTP	Center for Tobacco Products
ID	Idaho
MT	Montana
MTSS	Motivation To Stop Scale
NM	New Mexico
NV	Nevada
OR	Oregon
PATH	Population Assessment of Tobacco and Health
PMTA	Premarket Tobacco Product Application
Respondents	Total sample which includes ZYN [®] users and ZYN [®] non-users
SAP	Statistical Analysis Plan
SAS [®]	Statistical Analysis System
SMNA	Swedish Match North America
TNP	Tobacco/Nicotine Product
U.S.	United States
UT	Utah
WA	Washington
WY	Wyoming
ZYN [®] non-users	ZYN [®] non-users who use tobacco products

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STATISTICAL ANALYSIS PLAN

ZYN® Patterns of Use

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2. RESPONSIBLE PARTIES

2.1 Investigator and Contributors

Investigator:

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Project Team:

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2.1 Sponsor:

Swedish Match North America

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3. STATISTICAL ANALYSIS PLAN (SAP) AMENDMENTS AND UPDATES

Number	Date	Section of SAP	Amendment or Update	Reason
1	06/06/2018	Table shells	Amendment	Format edits to the table shells and accompanying footnotes were made for better representation and accuracy.
...				

4. BACKGROUND AND RATIONALE

In 2009, the Family Smoking Prevention and Tobacco Control Act was signed into law, giving the FDA the power to regulate the tobacco industry and establishing the Center for Tobacco Products (CTP) within the FDA. This law gives the CTP authority to regulate the marketing/advertising content and sale of tobacco/nicotine products^a (TNP). The FDA requires that the marketing of a new tobacco product be appropriate for the protection of the public health as determined “on the basis of well-controlled investigations” (Section 910).¹

The CTP has provided draft guidance on data for human studies designed to evaluate the risks and benefits to the population as a whole, including users and non-users of the tobacco product.^{1,2} Essentially, CTP will require researched-based evidence that, in general, (1) existing tobacco product users do not increase consumption; (2) non-tobacco users do not start using and (3) former tobacco users do not re-start use of tobacco.¹ Products marketed in the U.S. after February 15, 2007 must obtain a marketing authorization from the FDA, (i.e., through a premarket tobacco product application [PMTA] application or a Substantial Equivalence [SE] report) or they can no longer be sold in the U.S.^{1,2}

Swedish Match North America (SMNA) began selling ZYN[®] in 2014. ZYN[®] delivers nicotine derived from tobacco, but the ZYN[®] product itself does not contain tobacco leaves. It comes in a small pouch that contains nicotine flavoring elements and other ingredients required to ensure shelf stability. SMNA has no current intention of marketing ZYN[®] as a smoking cessation product, but rather as a nicotine-delivery product that requires no spitting, produces no off-putting odors, is smoke-free, and comes in a variety of flavors and nicotine strengths. As a result of the Tobacco Control Act requirements, SMNA must submit a PMTA to continue marketing the ZYN[®] product. The output of this research will be submitted to the FDA as part of the ZYN[®] PMTA.

5. OBJECTIVES

The overarching research questions within this project can be stated as follows: (i) *How do ZYN[®] users and ZYN[®] non-users use TNP, and (ii) how do they perceive health risks associated with TNP?* These questions will be studied by means of a retrospective assessment of TNP use among both ZYN[®] users and ZYN[®] non-users (the Retrospective Study); all study participants are of legal age to use TNP in their residential geography. Included as part of this project is a 10-week prospective study among ZYN[®] users and ZYN[®] non-users (the Prospective Study); SMNA is including objectives and related findings from the Prospective Study as part of the secondary objectives, since SMNA cannot guarantee a specific sample size or composition from that study. No formal hypotheses are specified for the ZYN[®] Patterns of Use Study.

^a “Tobacco/nicotine products” (TNP) refers to any combination of the following products: cigarettes, e-cigarettes, moist snuff, chewing tobacco, snus, nicotine pouches, cigars, cigarillos, and filtered cigars filled with tobacco, pipe tobacco, hookah and water pipe tobacco, and aids to help stop smoking. This list of tobacco/nicotine products defining TNP is based on the Population Assessment of Tobacco and Health.

5.1 Primary Objectives

Utilizing data from the Retrospective Study:

1. Compare TNP patterns of use between ZYN® users and ZYN® non-users over the past 30 days.

The study will examine usage patterns among respondents and, in particular, examine how ZYN® users utilize other TNP products, compared with ZYN® non-users. Of specific interest will be usage patterns of cigarettes, smokeless tobacco, aids to help stop smoking, and ZYN® itself.

2. Among ZYN® users, compare TNP patterns of use over the last 30 days with TNP patterns of use during the weeks prior to using ZYN®.

Within the cohort of ZYN® users, the study will explore how usage of TNP products might have changed from the period prior to starting ZYN® to the last 30 days. Of particular interest will be whether usage of ZYN® offsets usage of products such as cigarettes and smokeless tobacco.

3. Evaluate the level of compliance among ZYN® users with ZYN® usage instruction over the last seven days.

Focusing on the last seven days, the study will explore how ZYN® users report using the product. Specifically of interest will be compliance with usage instructions and presence/absence of product misuse.

5.2 Secondary Objectives

Utilizing data from the Retrospective Study:

1. Assess perceptions of absolute risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) among ZYN® users and ZYN® non-users.

The study will measure the perceived risk of the aforementioned health conditions attributed to using only ZYN® daily, smoking only cigarettes daily, and never having used any TNPs. Discussion sections will highlight any observed divergence between ZYN® users with ZYN® non-users.

2. Assess ZYN® users' perceptions of relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) associated with ZYN® as compared with using other TNP, aids that help stop smoking, and never having used any TNPs.

The study will measure the perceived risk of the aforementioned health conditions attributed to using only ZYN® daily relative to using only other TNP daily, daily use of aids to help stop smoking, or never having used any TNPs.

3. Assess ZYN® users' perceptions of relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) associated with adding ZYN® use to existing TNP use.

The study will measure the perceived relative risk of the aforementioned health conditions attributed to using both ZYN® and other TNP compared with using other TNP alone. From there, further analysis will delve into how adding ZYN® to existing TNP use alters perceived risk.

4. Assess ZYN® users' perceptions of relative risk of certain health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems, separately) to a person who quits use of all TNP compared with a person who quits all TNP except for daily use of ZYN®.

The study will measure the perceived relative risk of the aforementioned health conditions attributed to quitting all TNP except for the daily use of ZYN® compared with quitting all TNP use.

Utilizing data from the Prospective Study:

5. Explore daily TNP patterns of use among ZYN® users and ZYN® non-users, including reasons for ZYN® use, over a prospective 10-week observational period.
6. Compare the tendencies of ZYN® users to quit TNP or use the product in an incremental fashion, in a supplemental fashion, or in complete substitution of other TNP.

6. OVERALL STUDY DESIGN

6.1 Study Design

The ZYN® Patterns of Use Study consists of two separate projects, meant to gain an understanding of how ZYN® is and has been used among consumers. Each project includes ZYN® users and non-users, to allow for more informed investigation. Each study relies upon its own survey instrument; cognitive interviews informed retrospective and prospective surveys to ensure clear communication of survey items to respondents. The Retrospective Study utilizes a cross-sectional design to measure recalled TNP usage among ZYN® users and ZYN® non-users. The Prospective Study longitudinally evaluates TNP patterns of use among ZYN® users and ZYN® non-users over a 10-week observation period.

Due to the low incidence of ZYN® users among the general population, ZYN® user groups will be recruited directly from purchasers of ZYN® through invitation stickers placed directly on ZYN® canisters. A third-party vendor will be hired to place the study invitation stickers on product packaging (i.e., each individual ZYN® canister) for all varieties of ZYN® available at retail, from November 27 – December 15, 2017. The sticker initiative targets approximately 4,500 retail stores carrying ZYN®

across the 11 states where ZYN® is sold^b. More information on recruitment of ZYN® users through the ZYN® invitation sticker initiative is available in the ZYN® Patterns of Use Study protocol.⁴

ZYN® non-users will be recruited through online consumer survey panels, including (b) (4) (b) (4) and (b) (4). Shortfalls in the demographic quotas of the ZYN® non-users will be supplemented by engaging a call center, Directions in Research, for telephone recruiting. When enrollment in the survey for the ZYN® user cohort reaches 40%, the (b) (4) fielding team^c will analyze the demographic characteristics of the data (i.e., age, gender, racial or ethnic background, and education). The demographic characteristics of ZYN® users will then be used to stratify the sample of the ZYN® non-users. By recruiting ZYN® non-users based on demographic criteria corresponding to enrolled ZYN® users, the sample recruitment plan is designed to provide matching populations regarding socio-demographic characteristics. Participants in the ZYN® Patterns of Use Study will only be those who meet inclusion and exclusion criteria (explained in Sections 6.2.1 and 6.2.2). More information on recruitment of ZYN® non-users is available in the ZYN® Patterns of Use Study protocol.³

After recruitment, ZYN® users and ZYN® non-users will access a 10-20 minute retrospective survey where participants are asked to self-report current TNP use. Upon completion of the retrospective survey, respondents are invited to participate in the Prospective Study. The Prospective Study survey instrument administered to ZYN® users and ZYN® non-users who accept the invitation to the Prospective Study consists of a daily survey and a biweekly survey. Only respondents completing all 10 weeks in the Prospective Study period will be included in the final analyses. Additionally, individuals participating in the Prospective Study will be allowed to miss up to two daily surveys in each week of the 10-week observational period. Failure to complete the minimum five daily surveys per week will result in that participant being removed from the study.

6.2 Study Cohorts

The study sample consists of the adult population of U.S. states where ZYN® is available in retail outlets (AZ, CA, CO, ID, MT, NM, NV, OR, UT, WA, WY), and who are of legal age for TNP use. To meet the objectives of the ZYN® Patterns of Use Study, the study will include respondents from the following cohorts described in Table 1. ZYN® users and ZYN® non-users will be defined by self-reported TNP use, with the criterion that ZYN® users will be required to have entered the survey by way of an invitation sticker placed on the ZYN® canister. The definition of TNP use, and the product types constituting TNP for this study, were adapted from the Population Assessment of Tobacco and Health (PATH) study⁴ and used to define only the ZYN® non-user cohort. In the PATH study, a threshold of lifetime use is established for cigarette use, which is having smoked 100+ cigarettes in a

^b Retail outlets account for 96% of all sales for ZYN® based on Swedish Match North America internal data.

^c The fielding team is distinct from the analytical team, which will remain blinded to the data until Statistical Analysis Plans are complete.

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lifetime and for all other TNP is based on recollection of ever using the TNP fairly regularly.⁴ Current use is based on now using the product every day or some days.⁴

Table 1. ZYN® Patterns of use study cohorts.

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6.2.1 Subject Selection: Inclusion Criteria

In addition to the already mentioned cohort definitions, respondents must meet all of the following criteria to be included in the study:

- Minimum legal age for TNP use per local state requirements
- Able to read and speak English
- Currently a resident of one of the 11 U.S. states where ZYN® is available in retail outlets (AZ, CA, CO, ID, MT, NM, NV, OR, UT, WA, WY)
- Individuals who provide electronic informed consent

6.2.2 Subject Selection: Exclusion Criteria

Respondents who meet any of the following criteria will be excluded from the study:

- Respond as “don’t know” or “decline to answer” to specific demographics (U.S. residency, state of residence, age, gender, racial or ethnic background, or education)
- Unwilling or unable to provide informed consent
- Individual employed in any of the following fields or professions: market research, marketing, advertising, employee of a TNP manufacture, or physician
- Individuals who have taken part in a consumer research study on tobacco in the past 2 weeks prior to the Retrospective Study

6.3 Precision Analysis

The ZYN Patterns of Use study will run in conjunction with a Likelihood of Use study; these studies in tandem provide the consumer research required to support the PMTA.

While the Patterns of Use study primarily asks questions meant to report behaviors, as opposed to providing opinions, the decision was made to mirror the Likelihood of Use sampling algorithm. Hence, the Patterns of Use study precision analysis was performed under the following assumptions: a confidence interval of 95% ($\alpha=.05$), a standard deviation of 3.74,^d a small interval half-width, and a probability of achieving the desired precision of .99.

6.4 Study Sample Size

The precision analysis suggested a sample size of (b) (4) per cohort in the Retrospective Study would be appropriate. (Note that the Likelihood of Use study mentioned in [Section 6.3](#), and its associated precision analysis, suggested a sample size of (b) (4) per cohort of interest.) In total, the planned study sample for the Retrospective Study is (b) (4) with (b) (4) respondents in each cohort. **Table 2** presents the sample size for each cohort, while also noting that sample sizes for the Prospective Study will be an undetermined subset of those completing the Retrospective Study, and will consist of only participants who complete all 10 weeks of the prospective observational period.

Table 2. Sample sizes for the Retrospective and Prospective Studies.

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^d The standard deviation used in these power calculations are taken from data provided by Swedish Match, "A market research report (January 2017)" which uses the Juster Scale to measure purchase intentions for moist snuff. The standard deviation is an average of the 3 standard deviations taken from Question #9, 13, and 17.

6.5 Variables of Relevance to the Study

6.5.1 Outcomes

Primary Objectives

Outcomes that will be used to evaluate the primary objectives are as follows:

Reported use in the last 30 days will be assessed by using one item observing frequency of use for each TNP currently used over the last 30 days. The item is based on the approach employed in PATH for observing current TNP use.⁴ Response options for frequency of use include “Every day,” “Some days,” “Not at all,” “Don’t know” and “Decline to answer.”

Intention to quit respective TNP will be assessed using one item for each TNP assessing intention to quit the respective TNP. Intention to quit TNPs will be measured using the Motivation to Stop Scale (MTSS).⁵ The MTSS consists of one item with seven response options ranging from 1 (lowest) to 7 (highest level of motivation to stop smoking), also including “Don’t know.” Scale developers found that odds of quit attempts increased linearly with increasing levels of motivation. In the current study, we use the MTSS both for assessing intention to quit cigarettes and for other TNPs. Consistent with published research using the MTSS, we will report the mean MTSS score.⁶ The MTSS was selected for use in the ZYN[®] Patterns of Use Study due to its brevity and validation as a strong and accurate predictor of quit attempts.⁵

Reported use in the weeks prior to initiating ZYN[®] usage will be assessed by using one item observing frequency of use for each TNP used by a respondent. The item is based on the approach employed in PATH for observing current TNP use.⁴ Response options for frequency of use include “Every day,” “Some days,” “Not at all,” “Don’t know” and “Decline to answer.”

Level of compliance with ZYN[®] usage instructions will be assessed using one custom^e item for each of four examples representing proper and improper ZYN[®] use. Items corresponding to proper use include “Placed a ZYN[®] pouch between my gum and upper lip” and “Used one ZYN[®] pouch at a time.” Items corresponding to improper use of ZYN[®] include “Used one ZYN[®] pouch for more than

^e Custom items were designed based on product design and features, and respective questions were validated through cognitive interviews, to ensure that the item was appropriate and sufficiently clear to respondents.

60 minutes” and “Cut the ZYN[®] pouch open and used the pouch contents.” Response options for each item include “Always,” “Sometimes,” “Never,” “Don’t know” and “Decline to answer.”

Secondary Objectives

Outcomes that will be used to evaluate the secondary objectives are as follows:

Perceptions of absolute risk will be assessed using a single-choice scale (5-point Likert scale, fully anchored; from 1= Very low chance to 5= Very high chance, also including “Don’t know” and “Decline to answer”) for each of four health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems). This scale was modified from the risk perception scale in HINTS.⁷

Perceptions of relative risk will be assessed using a single-choice scale (5-point Likert scale, fully anchored; from 1= A much lower chance to 5= A much higher chance, also including “Don’t know” and “Decline to answer”) for each of the four health conditions (adult tooth loss, gum disease, mouth cancer, and serious health problems), contrasting ZYN[®] use with several other risk exposures. The risk exposures to be assessed for each health condition include use of ZYN[®] versus the daily use of other TNP, aids to help stop smoking, and never having used any TNPs; and quitting all TNP relative to quitting all TNP except for ZYN[®]. This scale was modified from the risk perception scale used in HINTS.⁷

Average daily reported use during the prospective observational period will be assessed based on one item in the daily prospective survey assessing TNP use for each TNP: namely, the number of times each TNP was used in each day of the observational period. Observations of daily TNP use will be used to derive average daily use of each TNP per week in the 10-week observational period.

Weekly frequency of use during the prospective observational period will be derived based on one item in the daily prospective survey assessing TNP use for each TNP: namely, the number of times each TNP was used in each day of the observational period. These observations will be used to derive weekly frequency of use for each TNP. For example, respondents participating in the Prospective Study who report using a TNP every day for a given week based on non-missing daily surveys (e.g., usage for 5/5, 6/6, or 7/7 daily surveys) will be considered “Every day” users. Respondents participating in the Prospective Study who report using a TNP at least one day, but not every day, (e.g., usage for 1/5, 1/6, 3/6, 2/7, etc., daily surveys) based on non-missing daily surveys will be considered “Some days” users. Finally, respondents participating in the Prospective Study who do not report any TNP use based on non-missing daily surveys (e.g., usage for 0/5, 0/6, or 0/7 daily surveys) will be considered “Not at all” users. Derived outcomes based on the prospective survey items are based on the approach employed in PATH for observing current TNP use.⁴

Weekly use of ZYN[®] with other TNP will be derived based on one item in the daily prospective survey assessing TNP use for each TNP: namely, the number of times each TNP was used in each day

of the observational period. These observations will be used to derive whether respondents used ZYN® only, ZYN®+cigarettes, ZYN®+other TNP (excluding cigarettes), ZYN®+smokeless (i.e., moist snuff, chewing tobacco, or snus), ZYN®+snus, ZYN®+chewing tobacco, or ZYN®+moist snuff in each week of the 10-week observational period.

Intention to quit each TNP during the prospective observational period will be assessed using the MTSS,⁵ described in detail above.

Reasons for ZYN® use will be assessed using one item in the biweekly survey assessing why respondents had used ZYN®. Reasons for using ZYN® include:

- To help me reduce my cigarette smoking;
- To help me quit smoking cigarettes;
- To help me reduce my use of tobacco products other than cigarettes;
- To help me quit using tobacco products other than cigarettes;
- To use in environments where other tobacco/nicotine products are not considered appropriate (e.g. church, etc.);
- To use in environments where other tobacco/nicotine products are not allowed (e.g. airplane, etc.);
- Less harmful to my health than cigarettes;
- Less harmful to my health than other tobacco products, excluding cigarettes;
- To avoid spitting as required with other products
- To add variety to the products I use;
- Comes in flavors I like;
- Does not cause me to smell like smoke/tobacco;
- Comes in two different levels of nicotine strength;
- Less harmful for those around me than cigarettes;
- More acceptable to non-tobacco users;
- No one can tell when I am using it;
- I was just curious to see what it was like;
- Ease of use;
- Recommended by person who works in the store where I buy my TNP;
- None of the above. Additional response options include “Don’t know” and “Decline to answer.”

Percent of days ZYN[®] is used will be derived based on one item in the daily prospective survey assessing ZYN[®] usage. The item will report the number of ZYN[®] pouches used each day. The average percent of days ZYN[®] is used will be calculated as the percentage of non-missing days in each week where at least one ZYN[®] pouch was used.

Average number of ZYN[®] pouches used per day will be derived based on one item in the daily prospective survey assessing ZYN[®] usage. The item will report the number of ZYN[®] pouches used each day. The average number of ZYN[®] pouches used per day will be calculated as the average number of ZYN[®] pouches used for non-missing days in each week.

Average number of minutes ZYN[®] was kept in mouth will be derived based on one item in the daily prospective survey assessing ZYN[®] usage. The item will report the typical duration of time an individual ZYN[®] pouch was used in the given day. The average number of minutes ZYN[®] was kept in the mouth will be calculated based on the duration of time a typical ZYN[®] pouch was kept in the mouth for non-missing days in a given week.

Quitting all TNP use will be derived based on one item in the daily prospective survey assessing usage of each TNP, based on daily TNP use during weeks 1 and 2 as well as TNP usage patterns in the last 30 days of the observational period. In particular, respondent TNP use during weeks 1 and 2 will be used to establish TNP use at the beginning of the prospective observational period.^f Quitting TNP will be determined based on respondents reporting zero TNP use over weeks 9 and 10.

Complete substitution of TNP use will be derived based on one item in the daily prospective survey assessing usage of each TNP, based on daily TNP use during weeks 1 and 2 as well as weeks 9 and 10 of the prospective observational period. In particular, respondent TNP use during weeks 1 and 2 will be used to establish TNP use at the beginning of the prospective observational period. Similarly, TNP use during weeks 9 and 10 will be used to determine TNP use at the end of the prospective observational period. ZYN[®] users who used other TNP during weeks 1 and 2 of the prospective observational period but only ZYN[®] in weeks 9 and 10 will be considered to have completely substituted ZYN[®] in place of other TNP.^g

Summaries of the outcomes for primary and secondary objectives, including measurement domain, subcategories, measurement details, and metrics, are presented in [Tables 3-5, 6-11](#), respectively.

^f TNP use for the prospective observational period was defined based on TNP use over weeks 1 and 2 in order to capture individuals using TNP at least 2 times per month.

^g Completely substituting ZYN[®] in place of other TNP was defined based on TNP use over weeks 1 and 2 and 9 and 10 in order to capture behavioral change for individuals using TNP at least 2 times per month.

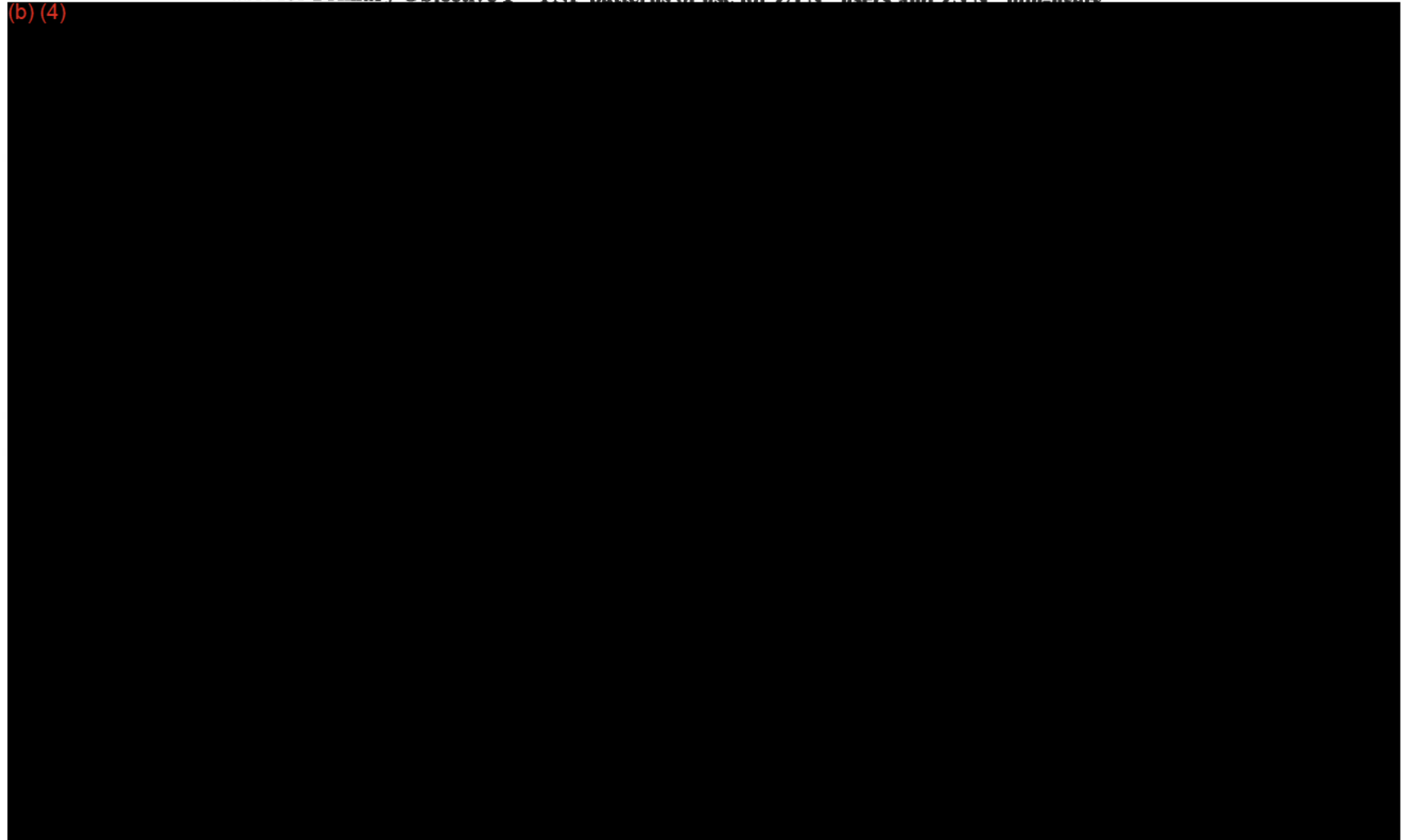
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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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Table 3. Outcomes Table for Primary Objective 1 – TNP patterns of use for ZYN® users and ZYN® non-users

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ZYN[®] Patterns of Use

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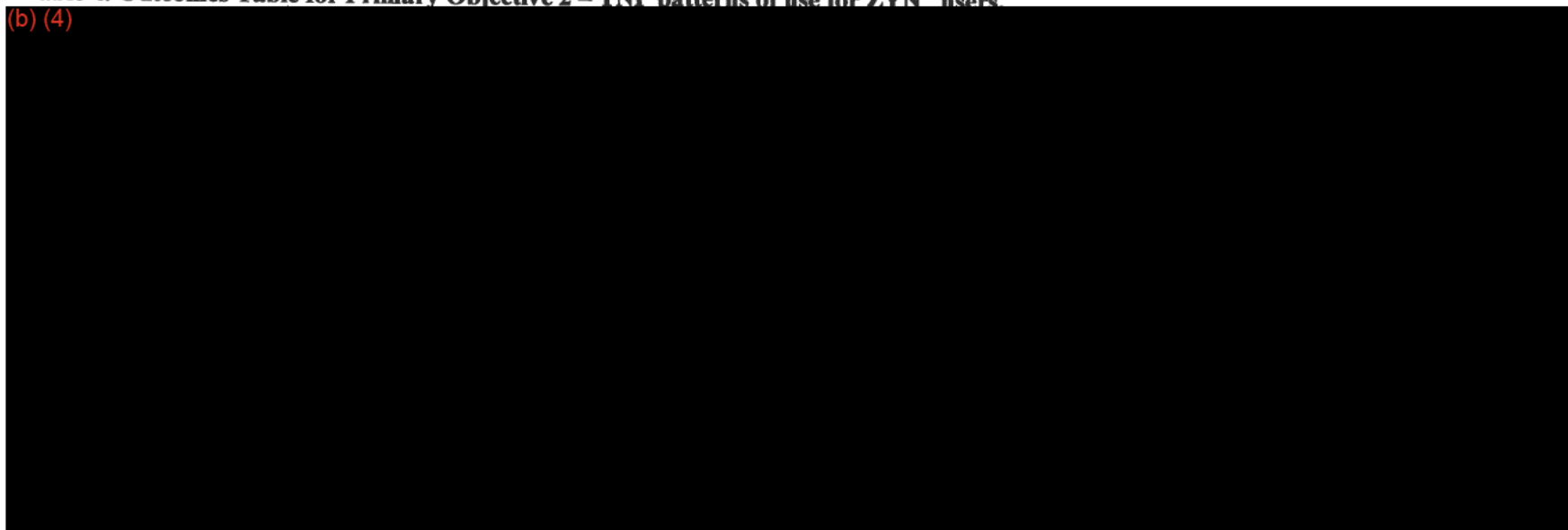
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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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Table 4. Outcomes Table for Primary Objective 2 – TNP patterns of use for ZYN[®] users

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Table 5. Outcomes Table for Primary Objective 3 – Compliance with ZYN[®] usage instructions.

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ZYN® Patterns of Use

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Table 6. Outcomes Table for Secondary Objective 1 – Percentions of absolute risk

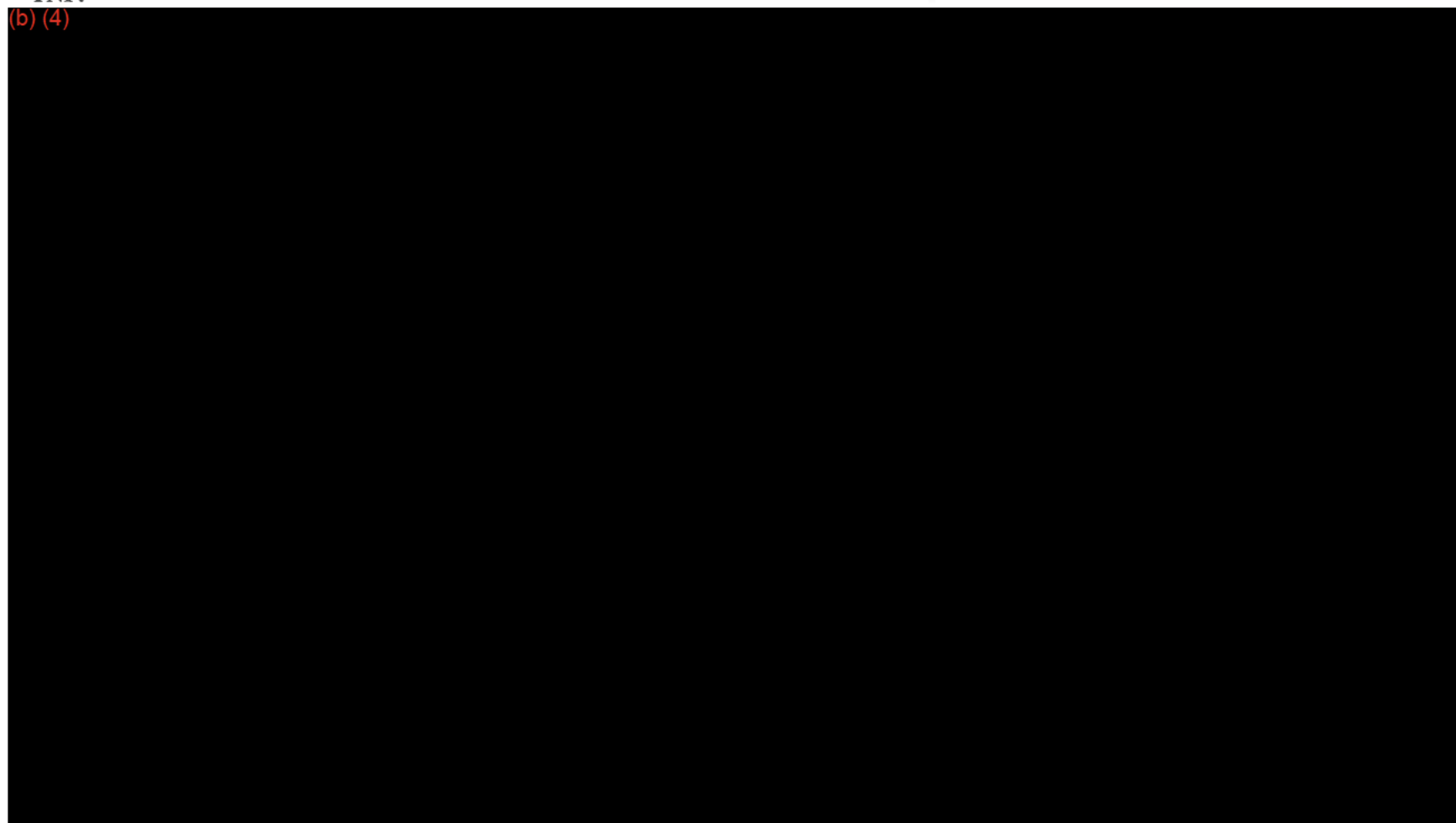
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Table 7. Outcomes Table for Secondary Objective 2 – Perceptions of relative risk, ZYN® relative to other TNP and never having used TNP.

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ZYN® Patterns of Use

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ZYN® Patterns of Use

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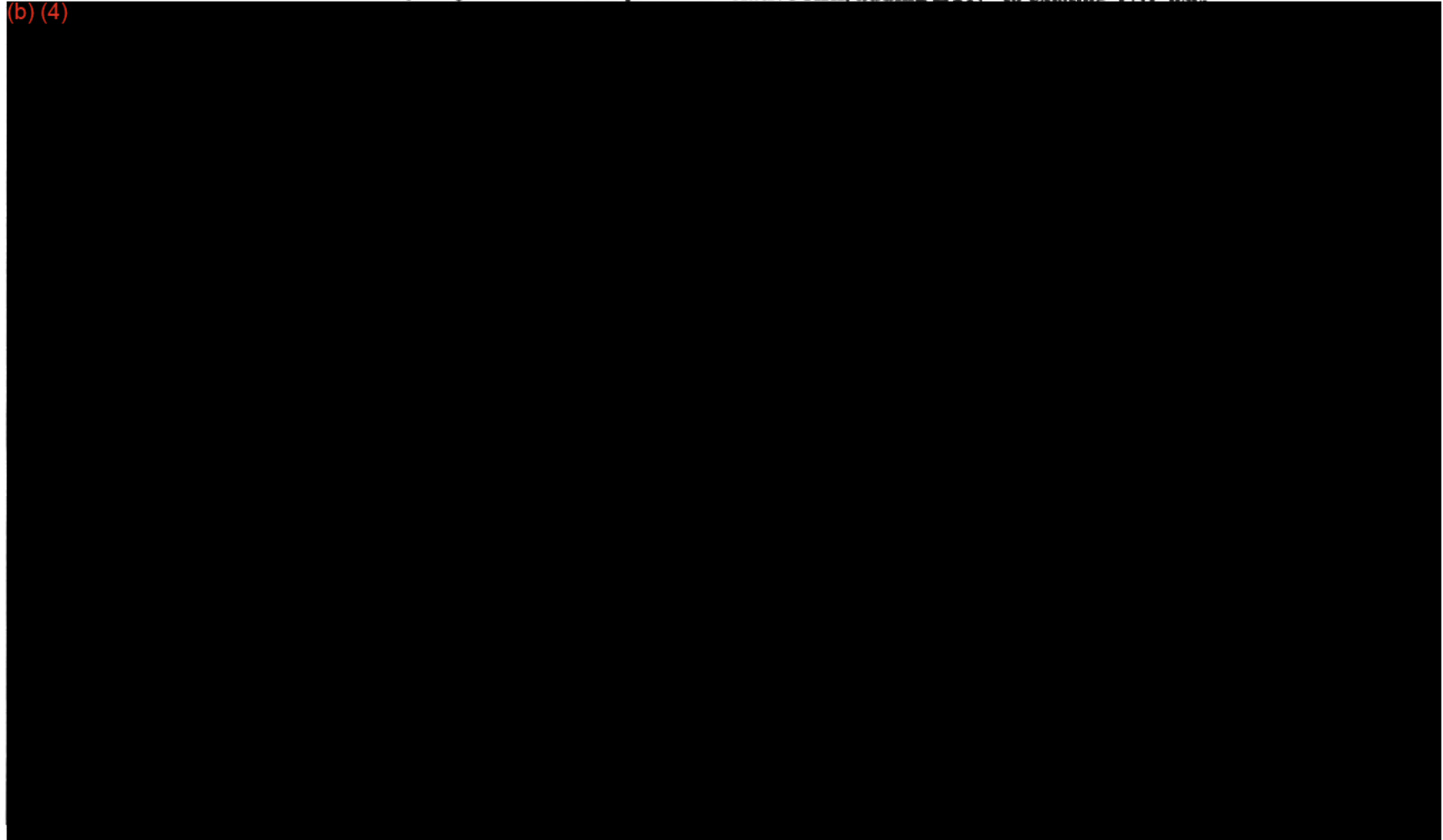
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ZYN® Patterns of Use

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Table 8. Outcomes Table for Secondary Objective 3 – Perceptions of relative risk, adding ZYN® to existing TNP use.

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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Table 9. Outcomes Table for Secondary Objective 4 – Perceptions of relative risk, ZYN[®] relative to quitting all TNP

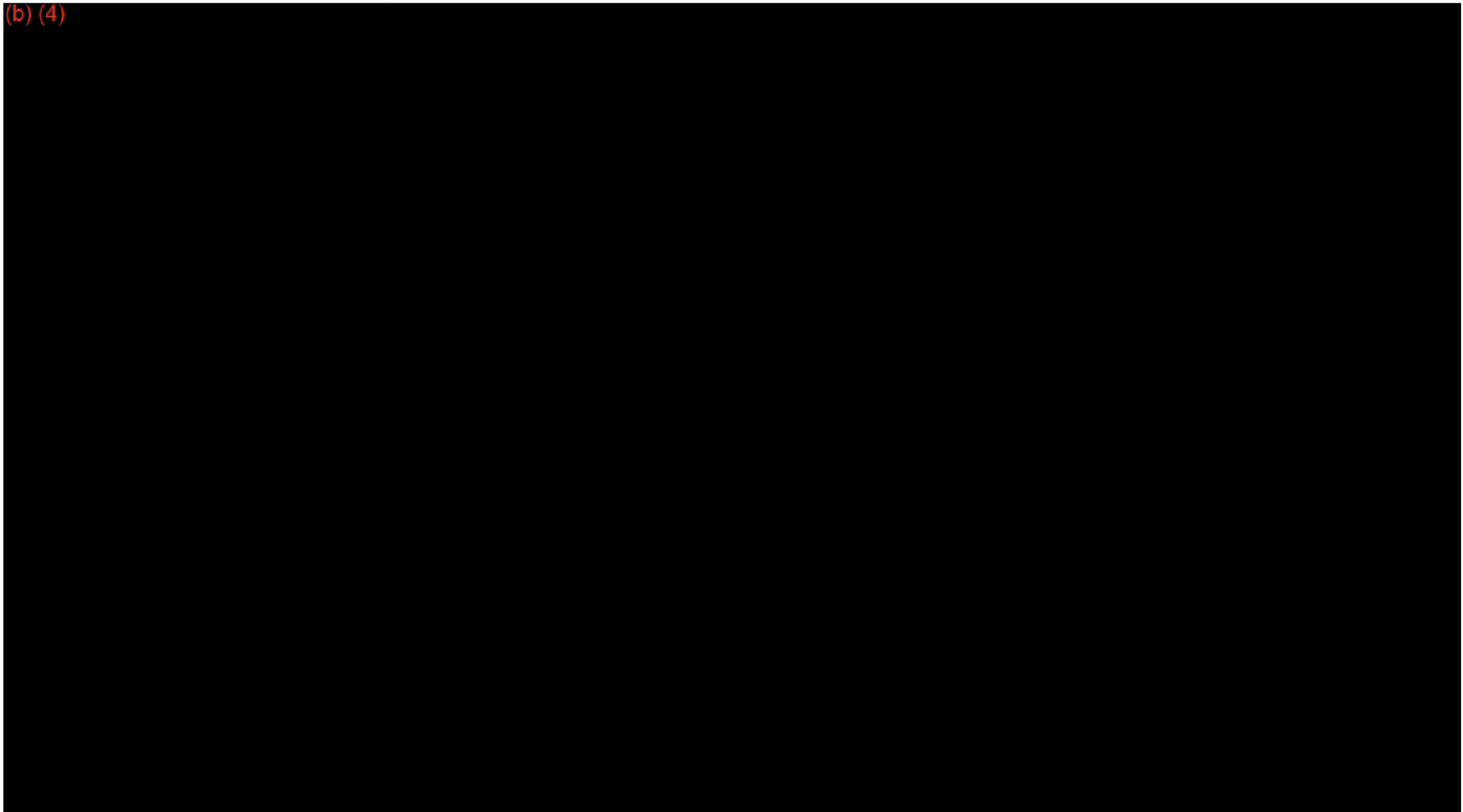
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Table 10. Outcomes Table for Secondary Objective 5 – Daily TNP patterns of use.

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ZYN[®] Patterns of Use

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ZYN[®] Patterns of Use

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ZYN® Patterns of Use

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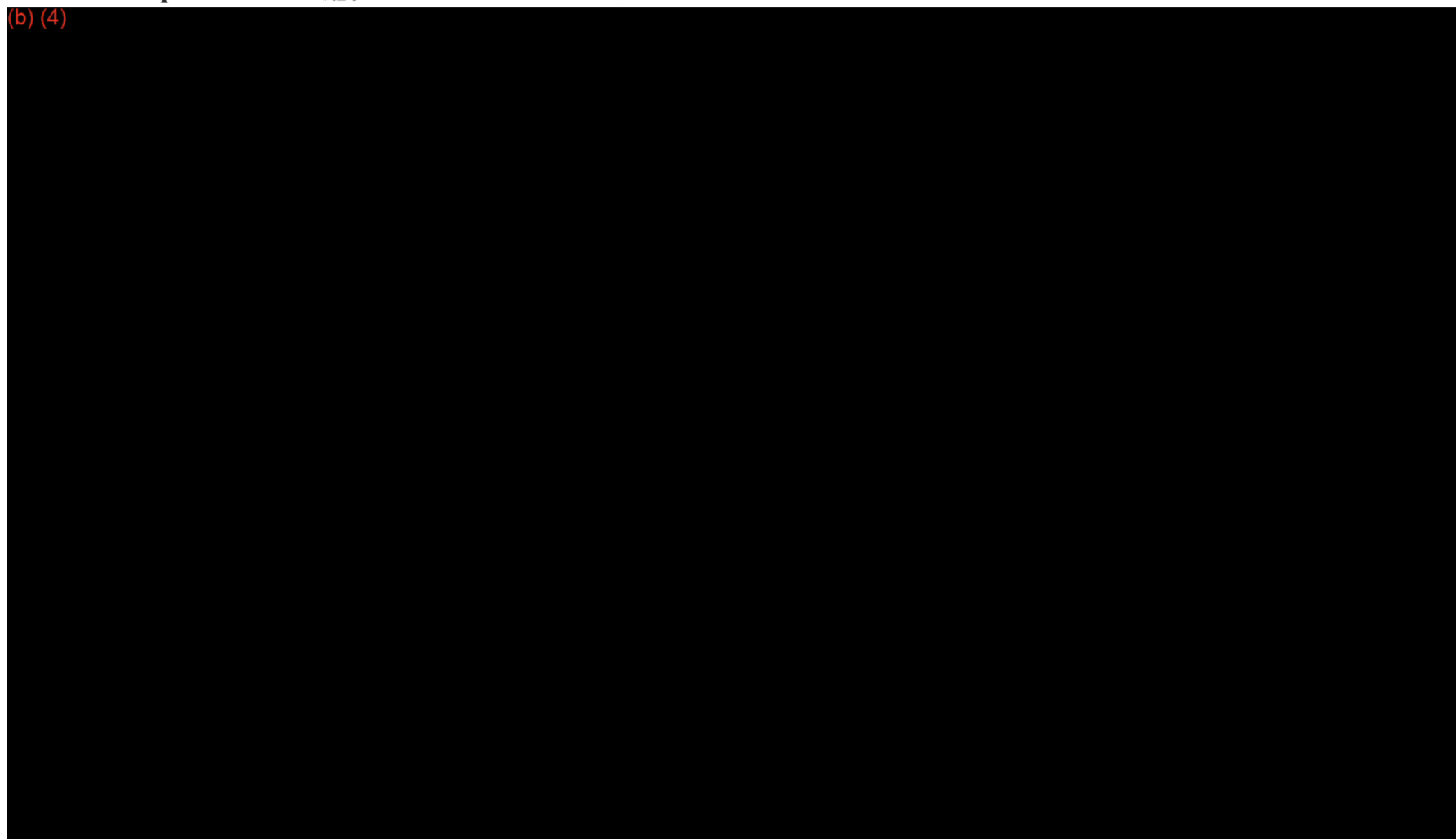
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ZYN® Patterns of Use

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Table 11. Outcomes Table for Secondary Objective 6 – Quitting TNP, incremental use, supplemental use, and completely substituting ZYN® in place of other TNP.*

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ZYN[®] Patterns of Use

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6.5.2 Respondent Characteristics

Socio-demographic Variables

State of residence, which will be assessed using a single item asking the respondent what state they spend most days of the year in. State of residence must be one of the eleven states in which ZYN® is sold (AZ, CA, CO, ID, OR, MT, NM, NV, UT, WA, or WY).

Age of the respondent will be assessed using a single item asking the respondent how many years old they are. Age of respondent will be categorized for reporting using the following age groups: 18-20, 21-24, 25-34, 35-44, 45-54, and 55+ years old.

Gender will be assessed using a single item asking the respondent if they are male or female.

Racial or ethnic background will be assessed using a single item asking the respondent which best describes their racial/ethnic background. Response options include: Caucasian/White, Black/African American, Hispanic (e.g., Latin American, Mexican, Puerto Rican, Cuban), Asian or Pacific Islander, Native American or Alaskan native, mixed racial background, other.

Highest grade or level of school completed will be assessed using a single item asking the respondent which response corresponds to the highest level of education they have attained. Response options include: Less than high school, some high school – no diploma, General Educational Development (GED), high school graduate – diploma, some college but no degree, Associate degree, Bachelor's degree (e.g., BA, AB, BS), Post-graduate degree (e.g., MBA, PhD, JD, etc.).

Marital Status will be assessed using a single item asking the respondent their marital status. Response options include: Now married, widowed, divorced, separated, never married, and decline to answer.

Number of adults who live in the household will be assessed using a single item asking the respondent for the number of individuals living in the household who are over 18 years old. Decline to answer is also available as a response option. Number of adults in the household will be categorized for reporting as 1, 2, 3, 4, or 5+.

Number of children who live in the household will be assessed using a single item asking the respondent for the number of individuals living in the household who are under 18 years old. Decline to answer is also available as a response option. Number of children in the household will be categorized for reporting as 1, 2, 3, 4, or 5+.

Household income in the last 12 months will be assessed using a single item asking respondents which category best describes their total household income in the last 12 months. Response options include: Less than \$10,000, \$10,000 to \$14,999, \$15,000 to \$24,999, \$25,000 to \$34,999, \$35,000 to \$49,999, \$50,000 to \$74,999, \$75,000 to \$99,999, \$100,000 to \$199,999, \$200,000 or more, don't know, or decline to answer. Household income will be categorized for reporting as less than \$25,000, \$25,000-49,999, \$50,000-74,999, \$75,000-99,999, \$100,000 or more.

6.6 Time Points of Importance

Time points of importance in the Retrospective Study occur under primary objective 1, TNP patterns of use. Specific time points of importance in the Retrospective Survey include the last 30 days, the weeks prior to starting ZYN®, and the last 7 days, which correspond to reported TNP use in the last 30 days, TNP use in the weeks prior to using ZYN® and compliance with ZYN® usage instructions over the last 7 days (both only among ZYN® users). Specific time points of importance in the Prospective Study include the prior day and the previous two weeks, which correspond to daily reported TNP use in the daily survey and intention to quit TNP in the biweekly survey.

7. STATISTICAL ANALYSIS

7.1 Presentation of Analysis Results

Numerical data will be presented by the total N-size, missing values (where applicable), mean, standard deviation (SD), median, minimums, and maximums. Numeric data, if reported as such, will be displayed to 2 decimal places. Otherwise, numeric data will be grouped into ranges and summarized by frequencies and percentages. Categorical data will be presented using frequencies (counts) and percentages; the number of missing values will also be presented (if applicable). Percentages will be displayed to 1 decimal place and counts with zero decimal places.

7.2 Study Analysis

All analyses performed for the ZYN® Patterns of Use Study will be descriptive in nature.

Descriptive statistics used to understand the distribution of socio-demographic and outcomes variables (see [Sections 6.5.1](#) and [6.5.2](#)) will be based on the raw data (i.e., prior to any recoding or any aggregation required for the final presentation of results). Respondents with values for variables that are illogical or deemed unreliable, as determined by the underlying distribution, will be considered for removal prior to performing the main analyses. (See [Section 8.2](#) and [8.3](#) for details regarding this process). Numeric variables will be described using total sample size, number of missing observations (if applicable), means, standard deviations, medians, minimums, and maximums. Categorical variables will be described using frequencies, percentages, and the number of missing observations (if applicable).

Unless otherwise specified in the table shells ([Section 10](#)), descriptive statistics reported for the main analyses will include the number of non-missing observations, means, standard deviations, and 95% confidence intervals (CIs), for numeric variables. For categorical variables it will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category.

The study team will format and properly label the data sets (including all responses from respondents and the date that the survey was completed) using SAS® software (Statistical Analysis System, version 9.3)⁸ so they are suitable for analysis. The data sets will contain a subject ID number and will not contain any information that could be used to identify individual respondents.

7.3 Socio-demographic Characteristics

Descriptive statistics will be reported for all socio-demographic variables outlined in [Section 6.5.2](#). Specifically, state of residence, age of respondent, gender, racial or ethnic background, highest grade

or level of school completed, marital status, number of adults who live in the household, number of children who live in the household, and household income in the last 12 months, will be reported for both ZYN® users and ZYN® non-users. **Table 21** presents a table shell showing how descriptive statistics for socio-demographic variables will be reported.

7.4 Primary Objectives

Descriptive statistics for accomplishing primary objectives will be reported for patterns of TNP use (for both ZYN® and ZYN® non-users) as well as compliance with ZYN® usage instructions among ZYN® users. Descriptive statistics will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category for categorical variables. **Tables 12 to 14** below provide summaries of the analyses that will be used to accomplish the primary objectives, including the objective, outcomes, cohorts, and the statistical analysis. **Tables 22 to 25** present table shells for reporting the results.

7.5 Secondary Objectives

Descriptive statistics for accomplishing secondary objectives utilizing data from the Retrospective Study will be reported for both perceptions of absolute risk and perceptions of relative risk. Descriptive statistics will include the number of non-missing observations, frequencies, percentages, and 95% CIs for the percentage of respondents endorsing each category, for categorical variables. **Tables 15 to 20** below provide summaries of the analyses that will be used to accomplish the secondary objectives, including the objective, outcomes, cohorts, and the statistical analysis. **Tables 26 to 29** present tables shells for reporting the results.

Descriptive statistics for accomplishing secondary objectives utilizing data from the Prospective Study will be reported for daily TNP patterns of use as well as incremental use, supplemental use, quitting all TNP excluding ZYN, and quitting all TNP including ZYN®. Descriptive statistics will include the number of non-missing observations, means, standard deviations, and 95% CIs. **Tables 19 and 20** below provide summaries of the analyses that will be used to accomplish the secondary objectives that are based on data from the Prospective Study, including the objective, outcomes, cohorts, and the statistical analysis. **Tables 30 to 37** present tables shells for reporting the results.

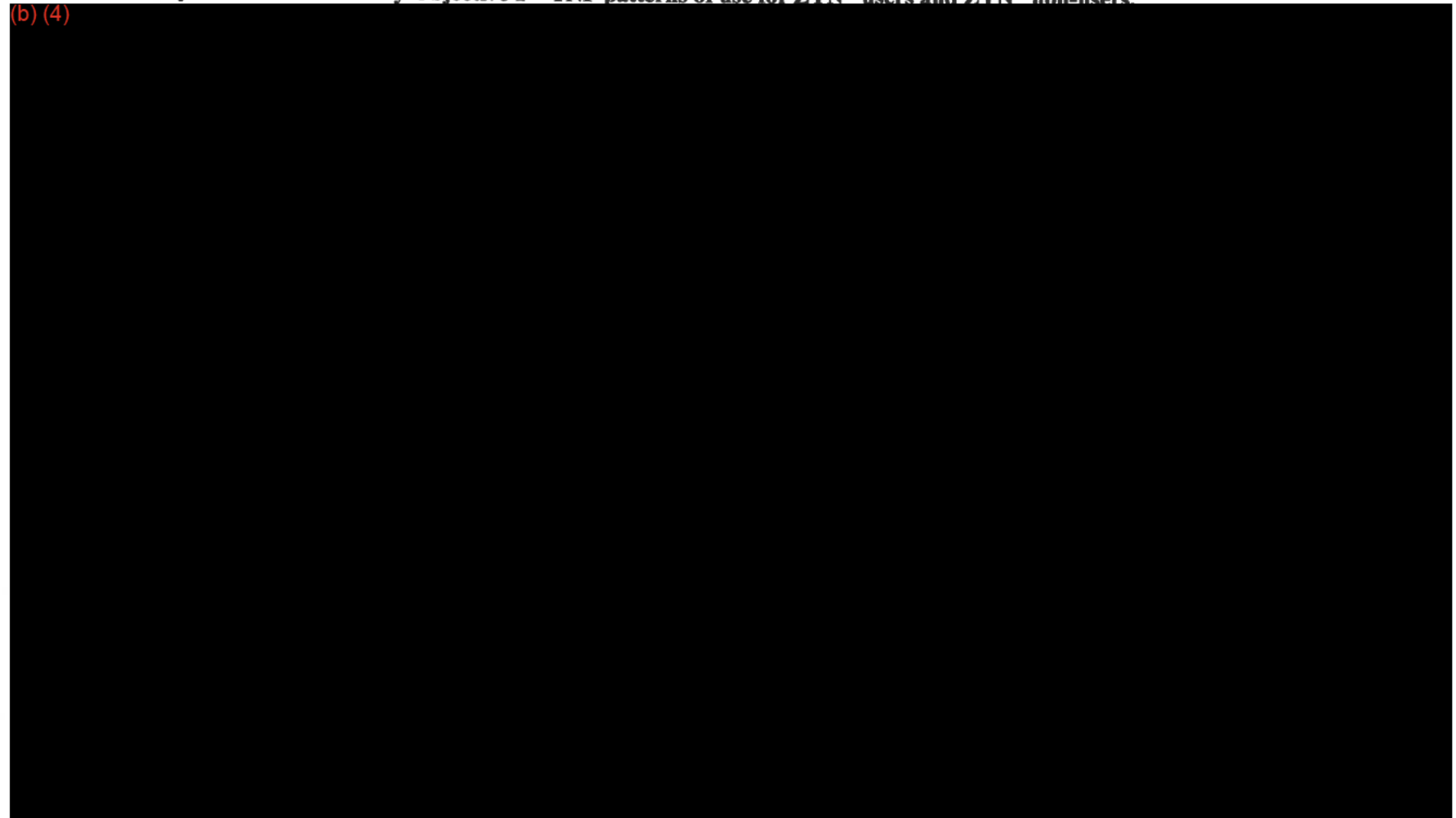
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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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Table 12. Analysis Table for Primary Objective 1 – TNP patterns of use for ZYN[®] users and ZYN[®] non-users.

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ZYN® Patterns of Use

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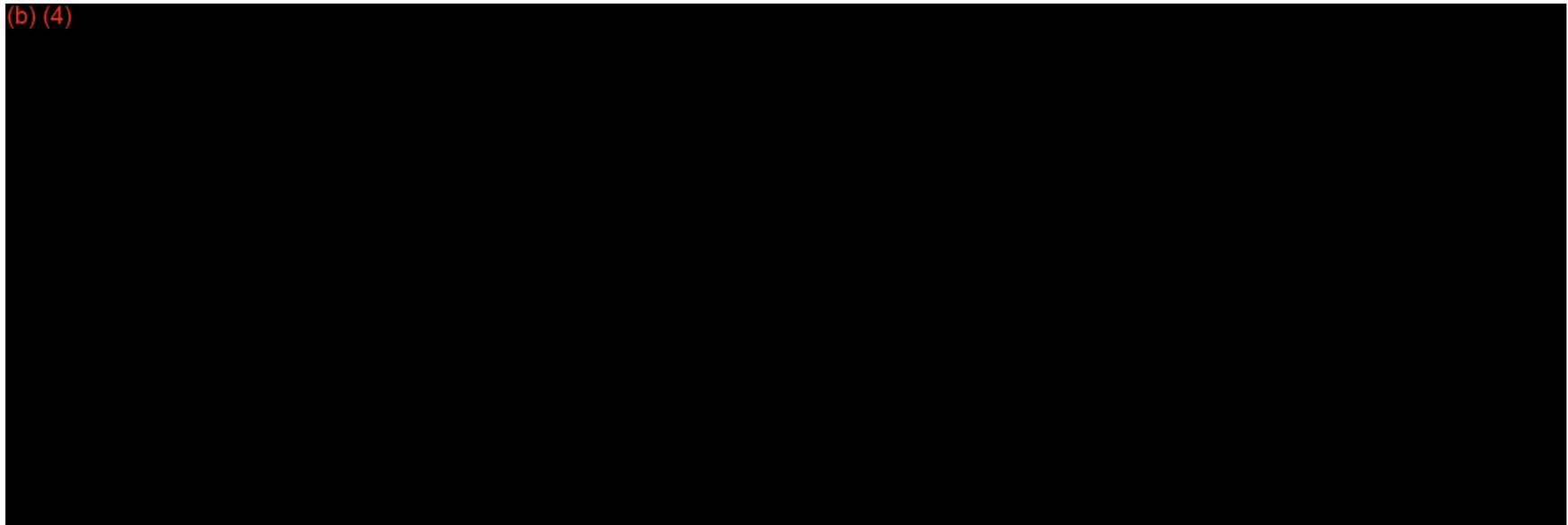
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Table 13. Analysis Table for Primary Objective 2 – TNP Patterns of use for ZYN® users.

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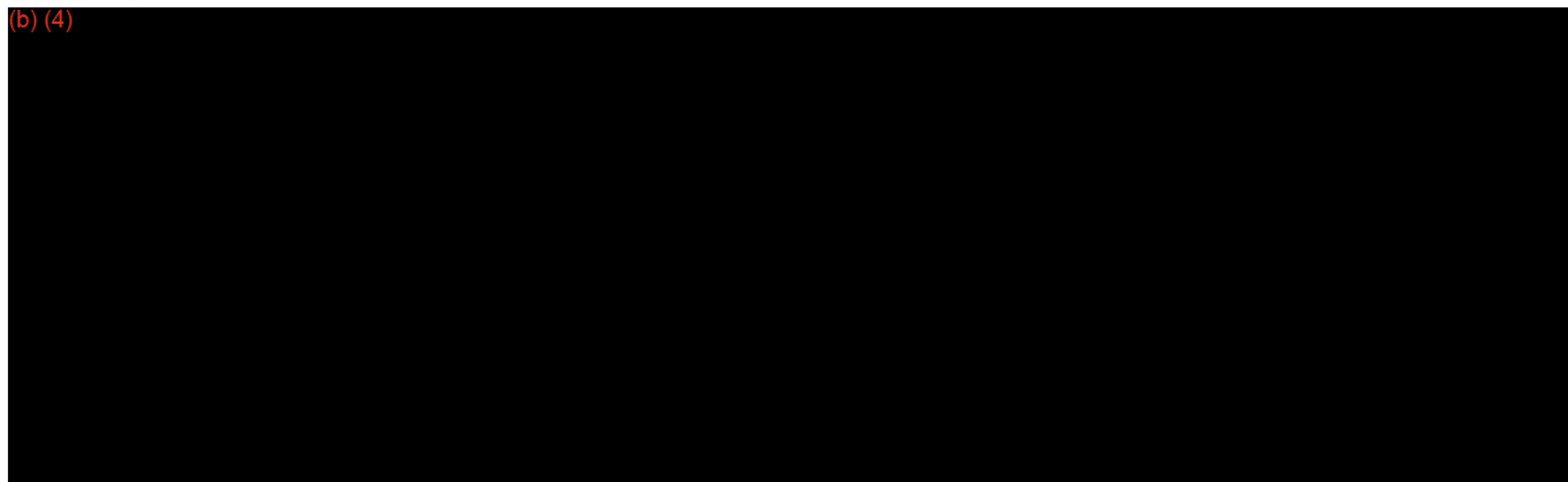


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Table 14. Analysis Table for Primary Objective 3 – Compliance with ZYN® usage instructions.

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ZYN® Patterns of Use

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Table 15. Analysis Table for Secondary Objective 1 – Perceptions of absolute risk.

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ZYN® Patterns of Use

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Table 16. Analysis Table for Secondary Objective 2 – Perceptions of relative risk, ZYN® relative to other TNP and never having used TNP.

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ZYN® Patterns of Use

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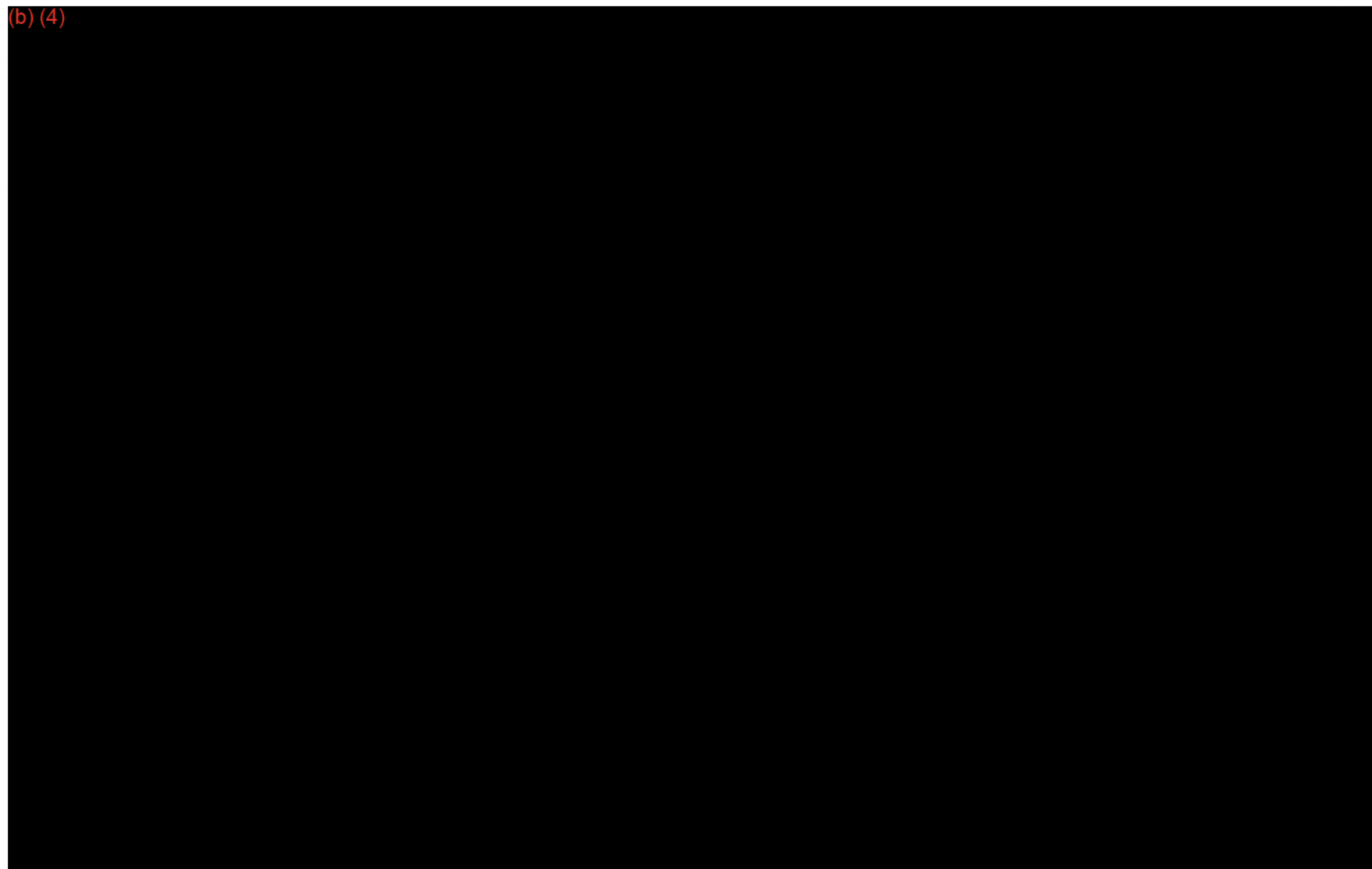
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ZYN® Patterns of Use

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ZYN® Patterns of Use

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Table 17. Analysis Table for Secondary Objective 3 – Perceptions of relative risk, adding ZYN® to existing TNP use.

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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Table 18. Analysis Table for Secondary Objective 4 – Perceptions of relative risk, ZYN® relative to quitting all TNP.

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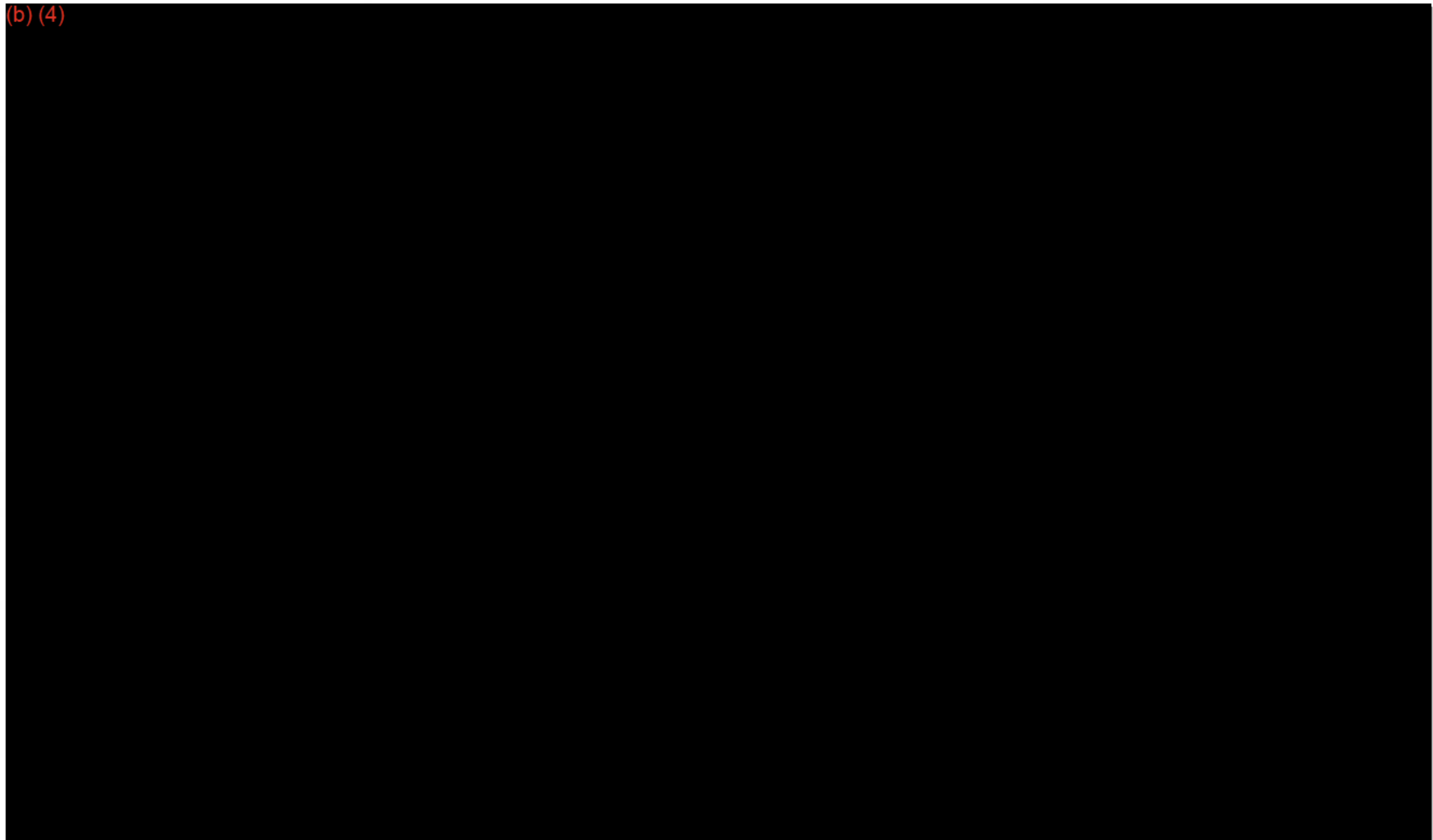


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Table 19. Analysis Table for Secondary Objective 5 – Daily TNP patterns of use for ZYN® Users and ZYN® Non-users.

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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ZYN[®] Patterns of Use

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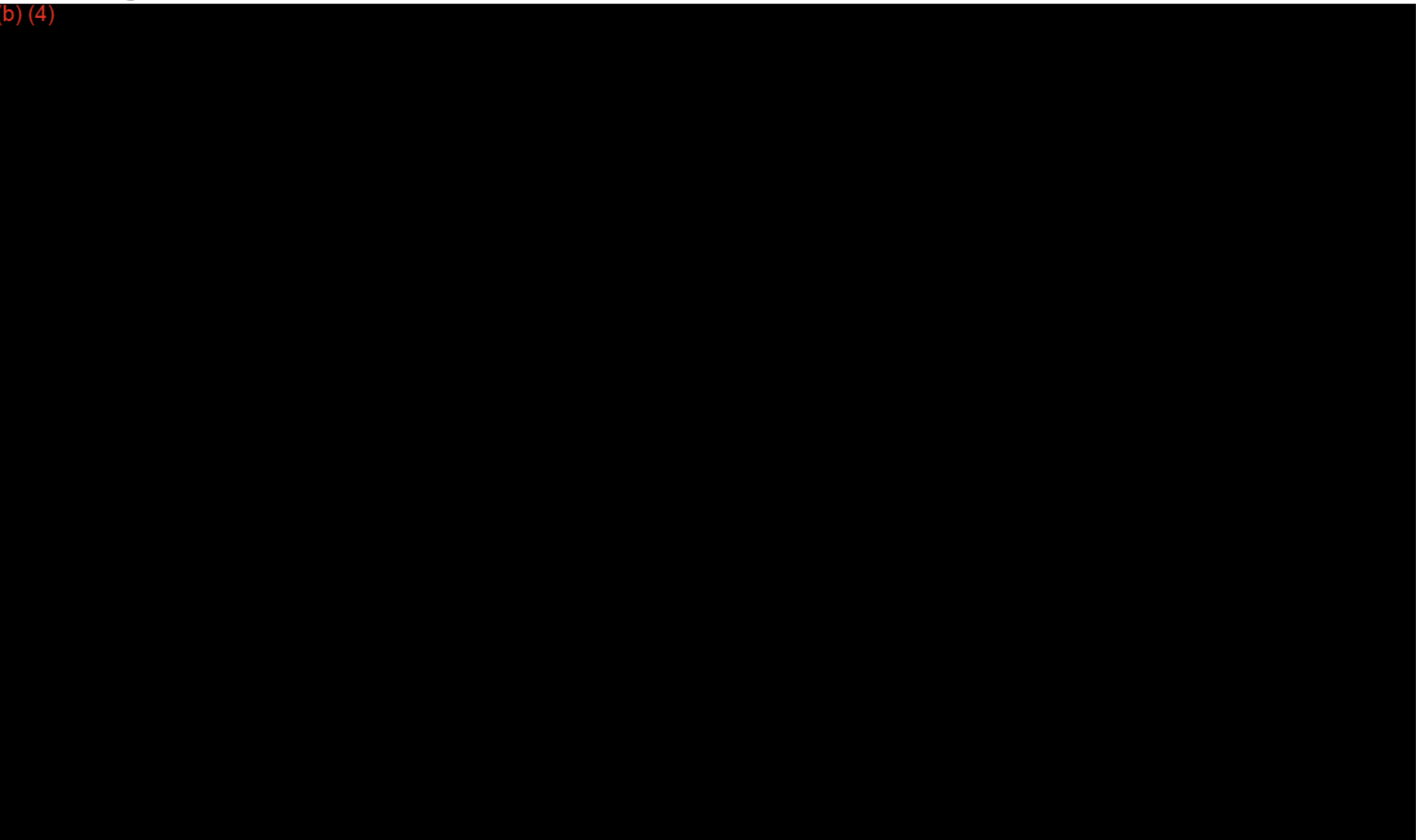
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Table 20. Analysis Table for Secondary Objective 6 – Supplemental, incremental, complete substitution of ZYN® in place of other TNP, and quitting TNP.

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ZYN[®] Patterns of Use

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8. STATISTICAL AND ANALYTICAL ISSUES

8.1 Data Capture and Management

8.1.1 Data Capture

The web-based survey will be created by the (b) (4) programming team using (b) (4) for web-based survey programming (b) (4). After the survey has been programmed and tested, the survey link and content will be reviewed by a separate team within (b) (4) fielding operations group from the perspective of the respondent (i.e. the link is reviewed online and not within the (b) (4)).

The data collected for this study will be monitored for adherence with the Study Protocol³. All data will be collected using a programmed web survey.⁹ Prior to initiating the study, appropriate edit programming will be conducted to assure the final dataset requires minimal cleaning of invalid responses. These programming procedures for the web-based survey data entry tool will include response ranges, consistency checks, skip patterns, and other special edit procedures where applicable. At every step of data processing, results or creating grouping variables will be cross-checked by (b) (4) (b) (4) operations team members who independently replicate the results and/or verify that the data have been handled appropriately and accurately. Any inconsistencies identified during this process are corrected before data are provided to (b) (4) analytical team to begin study analysis.

8.1.2 Data Management and Analysis QC Process

- Until the approval of the ZYN® Patterns of Use SAP by SMNA, the data will remain blinded and locked.
- Once data are unlocked, the analytical team will perform the following checks prior to conducting data analyses specified in the SAP:
 - The classification of participants into the study cohorts based on self-reported use or non-use of TNP will be confirmed.
 - Completion of the survey will be verified, and any respondent who did not complete the full survey will be removed from analysis.
 - It will be verified that respondents satisfied the inclusion and exclusion criteria.
 - The actual quota frequencies for each study cohort in the data set will be compared against the quota frequencies specified in the Study Protocol. Any discrepancies will be documented in the final report.
- All variable coding will follow as specified in the SAP (e.g., grouping age by age brackets, grouping the number of adults/children in the household, and total household income in the last 12 months).
- All statistical analyses and results output will be validated by another researcher on the analytical team for quality control. Validation will cover:
 - Correct coding of variables;

- Correct use of statistical methods as specified in the analysis section;
- Correct export of results from SAS® output to Excel tables.

8.2 Handling of Missing Data

The structure of the Retrospective Study questionnaire does not have “true” missing data. The online survey does not allow respondents to proceed without receiving an answer to the present question. No partially completed surveys will be included in the final Retrospective Study data set or Retrospective Study analyses. For the Retrospective Study, data points are either missing because the respondent selected “Don’t know” or “Decline to answer,” or they did not qualify to answer the question due to survey skip logic. Thus, these types of missing data will be kept as is and will be reported descriptively (percentages and counts). The questionnaire was designed (and tested through cognitive interviewing) so that instructions are as easy to understand and as clear as possible, to help avoid missing data.

Both the Prospective Study and Retrospective Study questionnaires do not allow respondents to proceed without answering the present question. Hence, missing observations for completed daily or biweekly surveys arise because the respondent selected “Don’t know” or “Decline to answer,” or s/he did not qualify to answer the question due to prior answers. No modifications will take place in these instances.

However, missing data in the Prospective Study can also arise from incomplete daily surveys. Study participants can remain in the study while failing to complete two daily surveys per week during the 10-week observational period. Data will be absent in those situations, i.e. the investigator will not impute values. Daily TNP patterns of use outcomes, such as average daily use for each TNP for a respondent in a week, will be calculated based on the number of non-missing entries. Specifically, if 5 entries are available for a respondent in a given week, then the respondent’s average daily use for each TNP for the week will be based on the average of the 5 available entries. Likewise, if 6 entries are available for a respondent in a given week, then the respondent’s average daily use for each TNP for the week will be based on the average of the 6 available entries.

The rationale and utilization of “Don’t know” and “Decline to answer” response options are as follows:

- In this study, a “Decline to answer” response option without a “Don’t Know” option will be provided for any question where there is personally sensitive information, but the answer would be known to the respondent (e.g., age, gender, etc.).
- “Don’t know” and “Decline to answer” options will be provided for all other questions.

8.3 Identification of Outliers

- When conducting online research, invariably some respondents will find a way to complete the survey without attempting to provide accurate, relevant responses. To ensure that those respondents do not compromise the integrity of the data, measures are taken to eliminate their data from consideration prior to actual analyses. This process requires objectivity and removes respondent data regardless of directionality. The process will seek to identify the following respondent types:

- Respondents who lack variability in their responses to a battery of questions (“straight liners”) will be identified using standard deviations customized for each battery found in the survey. Respondents whose responses have a standard deviation of zero or greater than four times the overall standard deviation will be flagged and examined individually.
- Similarly, respondents who demonstrate a discernable pattern in their answers inconsistent with any coherent understanding of the question (e.g., selecting 1, 2, 3, 4, 5, 1, 2, 3, 4, 5, 1... etc.) will also be flagged and examined individually. Respondents who are straight lining or giving patterned responses consistently throughout the survey (i.e., across multiple sections of the survey) will be individually scrutinized.
- Respondents found to lack credibility will be identified, handled consistently and transparently, and documented in the final report. This said, the *a priori* assumption is that all data reported is true and accurate, and preliminary outliers will be identified based on the underlying distribution of the data, and through descriptive analysis.
- Data from non-credible respondents will be flagged in the data file. Additionally, the number of respondents flagged and the rationale for their identification as outliers will be reported in the final report.
- Sensitivity analyses will be conducted for every outcome with the outliers removed. The results of the sensitivity analyses will be reported as to whether the exclusion of the outliers changed the descriptive results in a substantive way.
- Per the ZYN® Patterns of Use Study protocol,³ respondents who participate in the Prospective Study are required to complete at least 5 daily surveys in each week in the 10-week observational period. Accordingly, respondents who miss more than 2 daily surveys in a given week will be removed from the final locked data set, but will be retained in a separate complete data set.

9. REFERENCES

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8. Statistical Analysis Software (SAS). [Computer software]. SAS Institute, Cary NC.
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10. TABLE SHELLS

Table 21. Table Shell for the Socio-demographics of ZYN® users and ZYN® non-users.

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ZYN[®] Patterns of Use

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ZYN® Patterns of Use

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Table 22. Table Shell for Primary Objective 1 – TNP patterns of use for ZYN® users and ZYN® non-users. Reported TNP use in the last 30 days.

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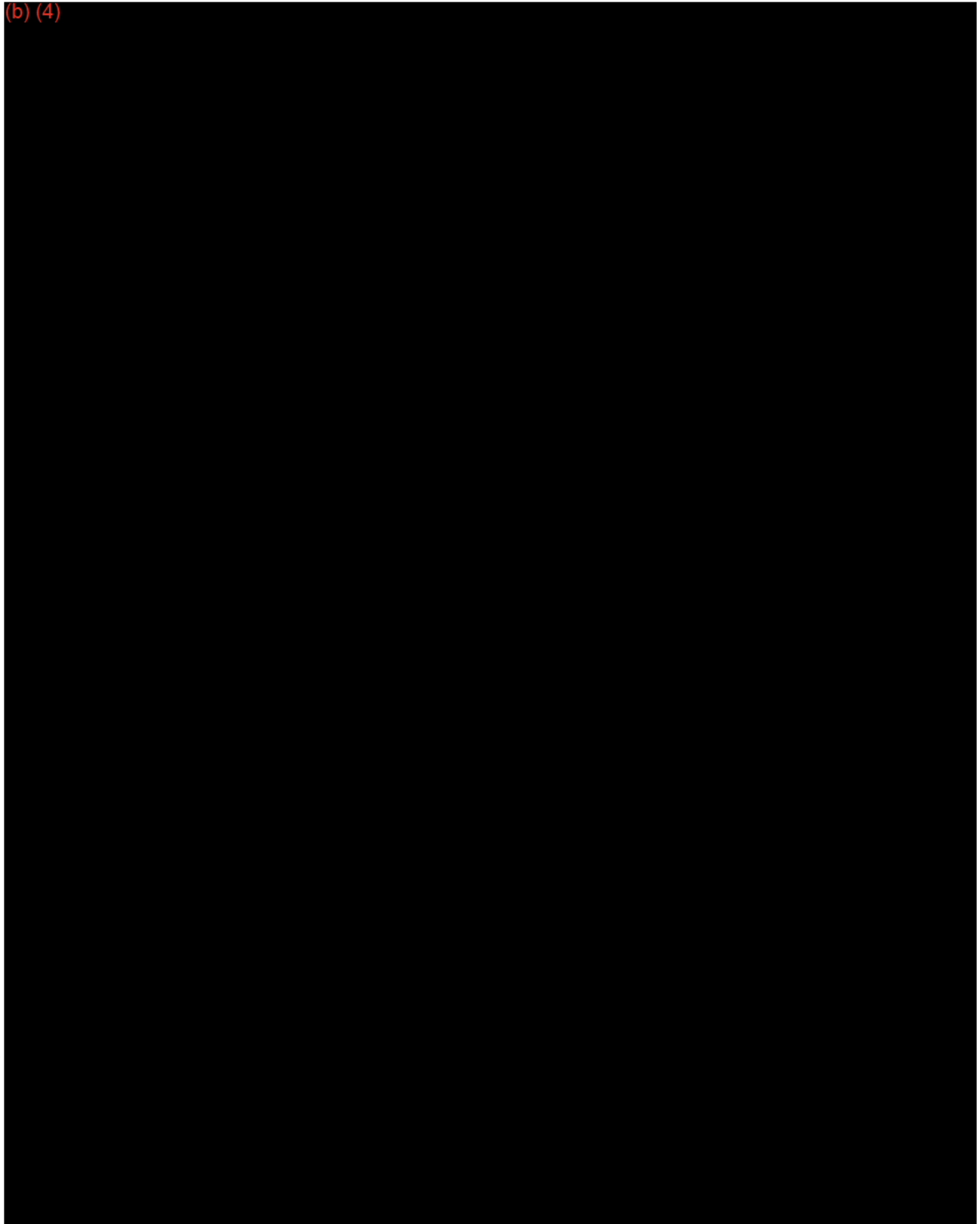
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Table 23. Table Shell for Primary Objective 1 – TNP patterns of use for ZYN® users and ZYN® non-users. Intention to quit TNP based on the Motivation to Stop Scale (MTSS).

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ZYN[®] Patterns of Use

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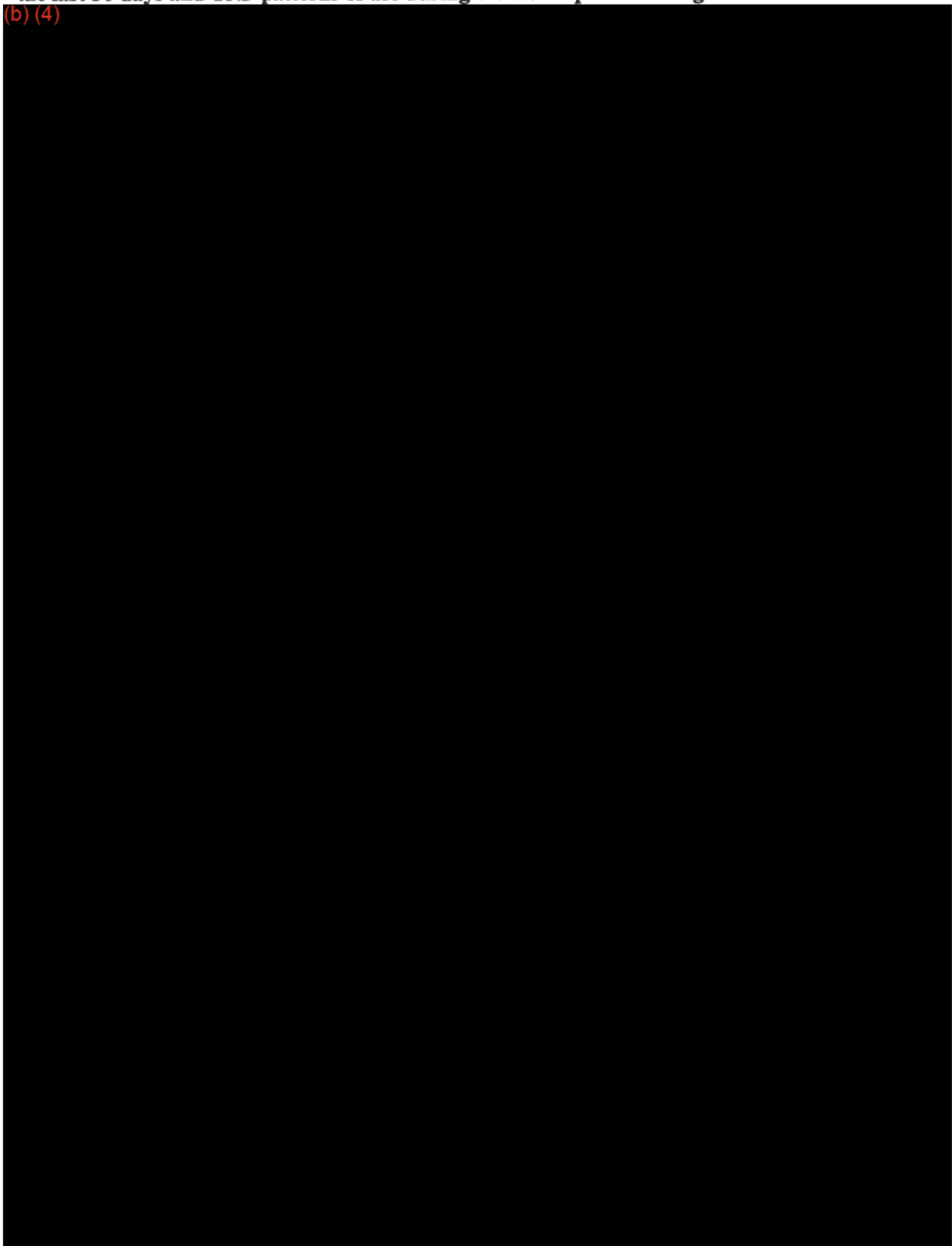
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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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Table 24. Table Shell for Primary Objective 2 – Among ZYN® users, TNP patterns of use over the last 30 days and TNP patterns of use during the weeks prior to using ZYN®.

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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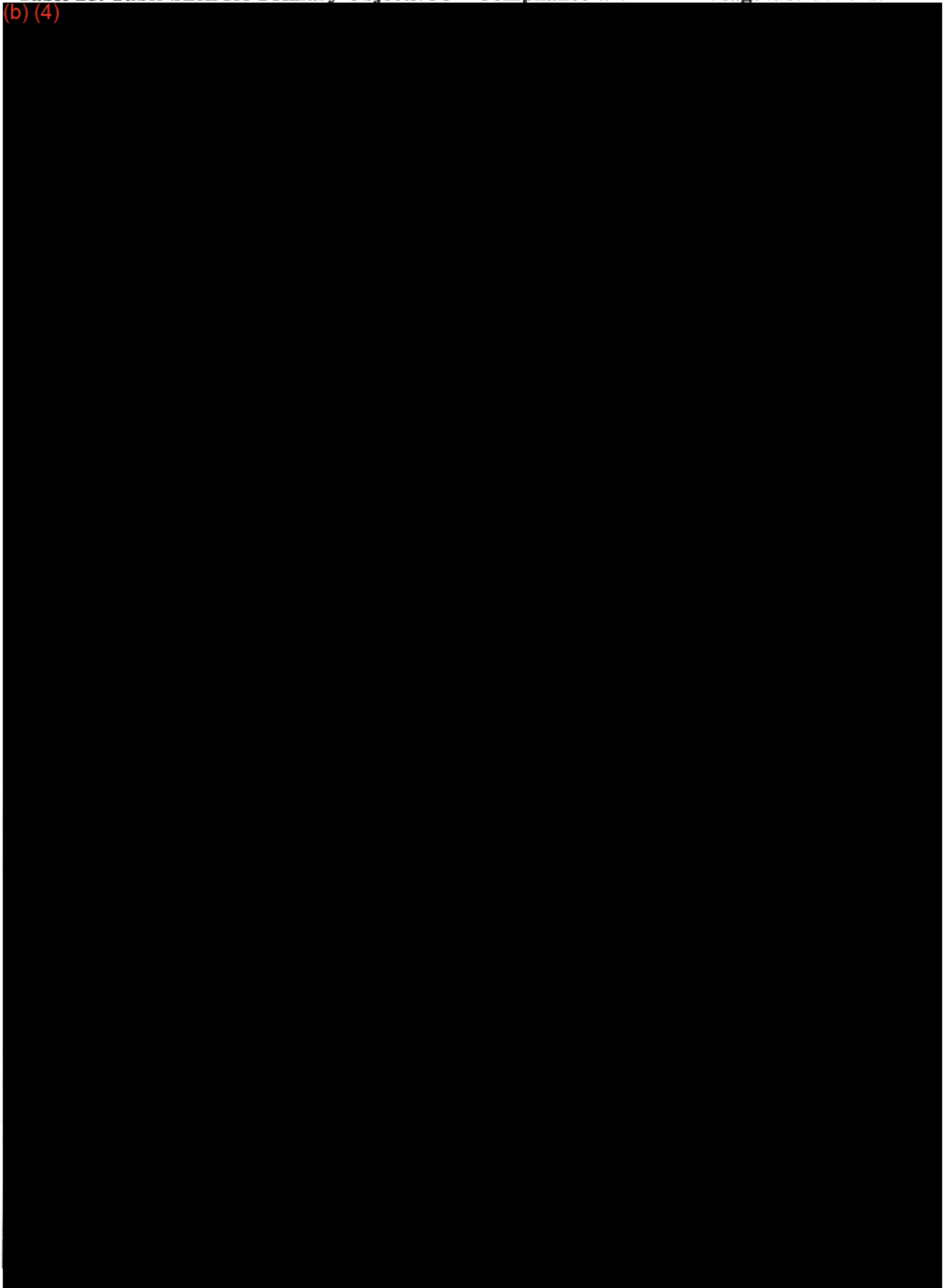
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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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Table 25. Table Shell for Primary Objective 3 – Compliance with ZYN[®] usage instructions.

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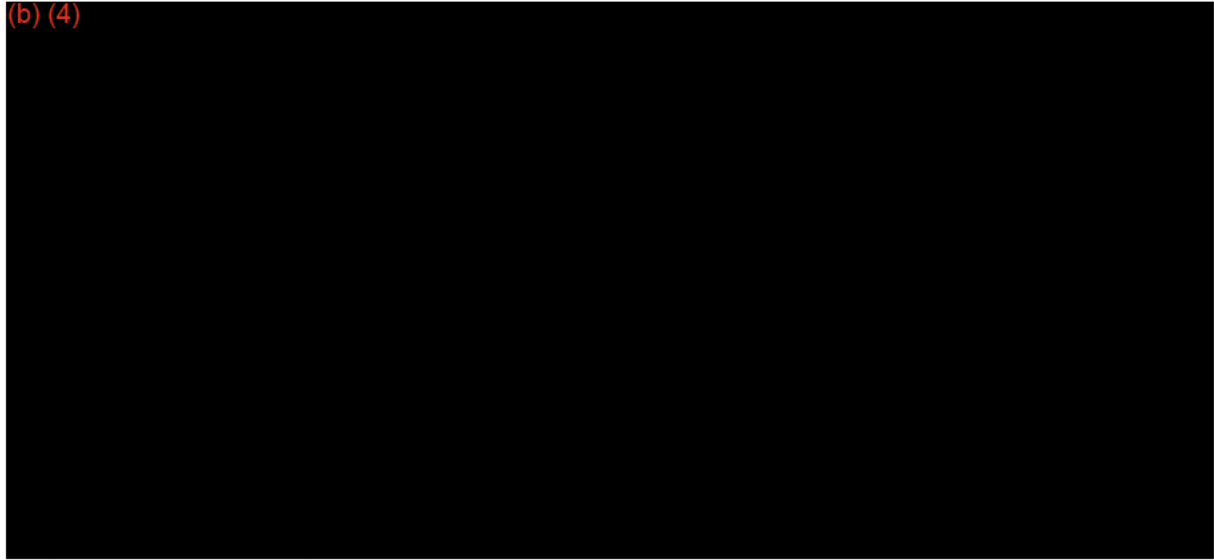


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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

(b) (4)

Table 26. Table Shell for Secondary Objective 1 – Perceptions of absolute risk.

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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Table 27. Table Shell for Secondary Objective 2 – Among ZYN[®] users, perceptions of the relative risk of ZYN[®].

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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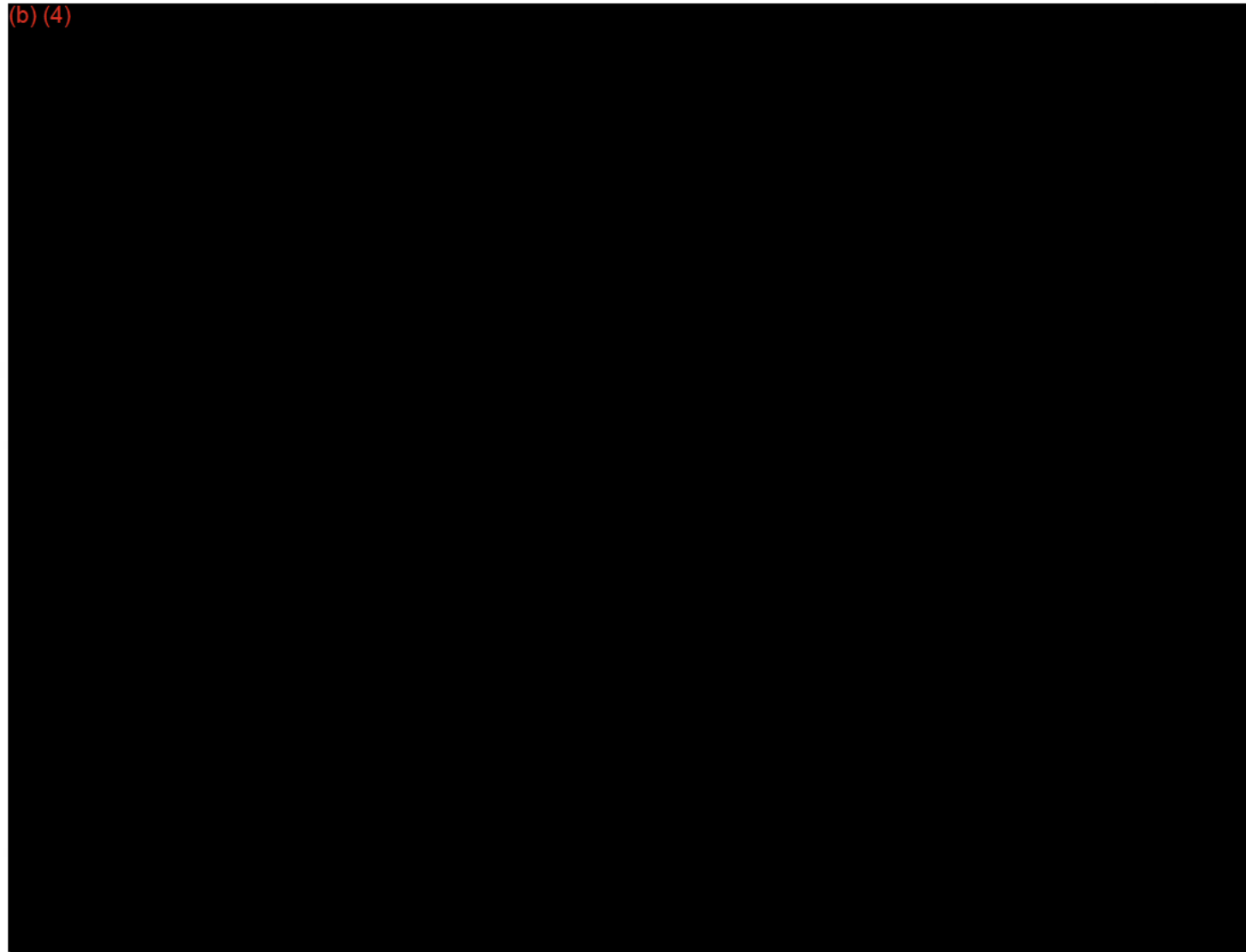
Confidential

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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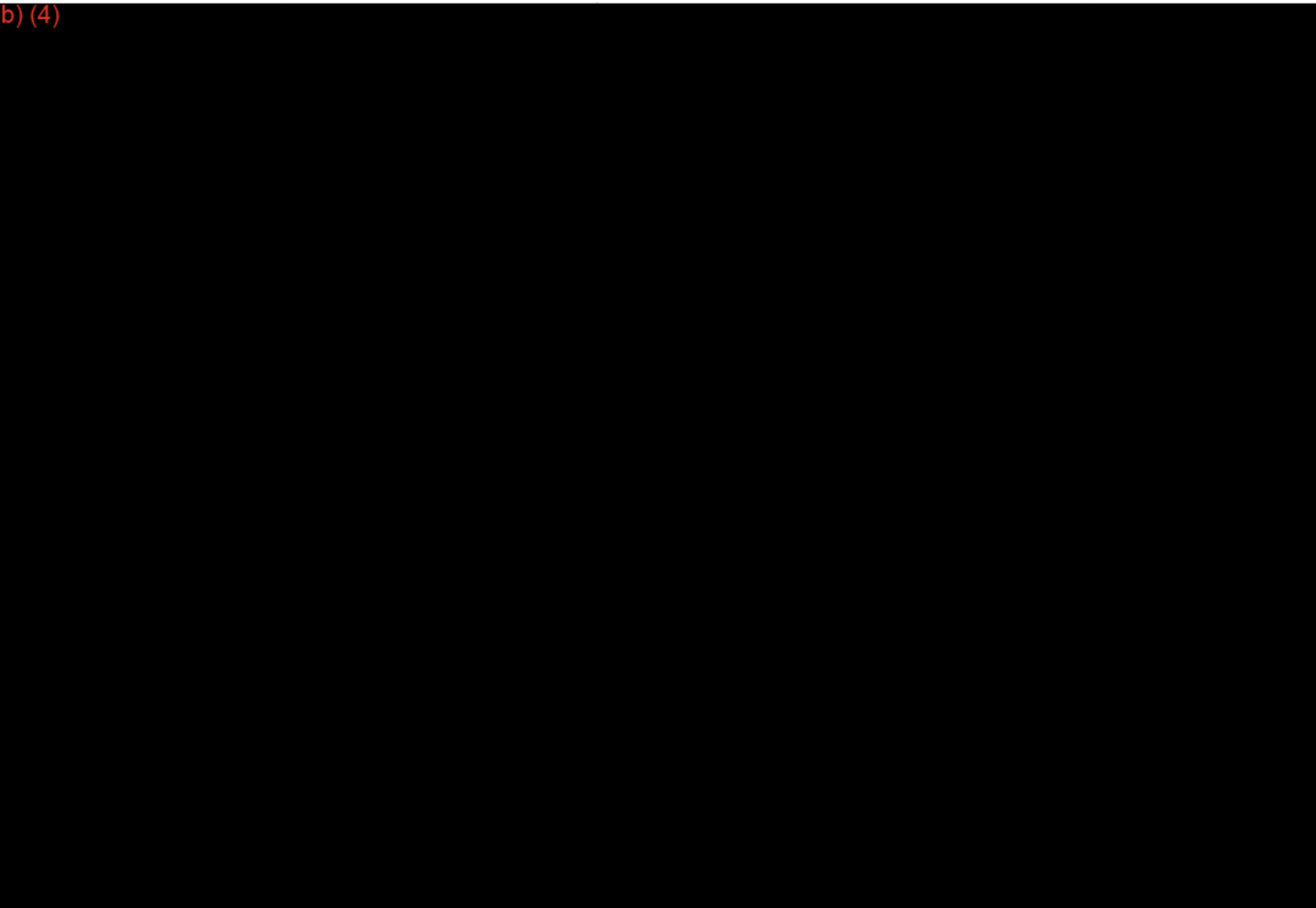
(b) (4)

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Table 28. Table Shell for Secondary Objective 3 – Among ZYN® users, perceptions of the relative risk of adding ZYN® to existing TNP use.

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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Confidential

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

(b) (4)

Table 29. Table Shell for Secondary Objective 4 – Among ZYN® users, perceptions of the relative risk of quitting all TNP except for ZYN® compared with quitting all TNP.

(b) (4)



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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

(b) (4)

Table 30. Table Shell for Secondary Objective 5 – TNP patterns of use among ZYN® users and ZYN® non-users based on the average daily reported TNP use for each week in prospective observational period.

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

(b) (4)

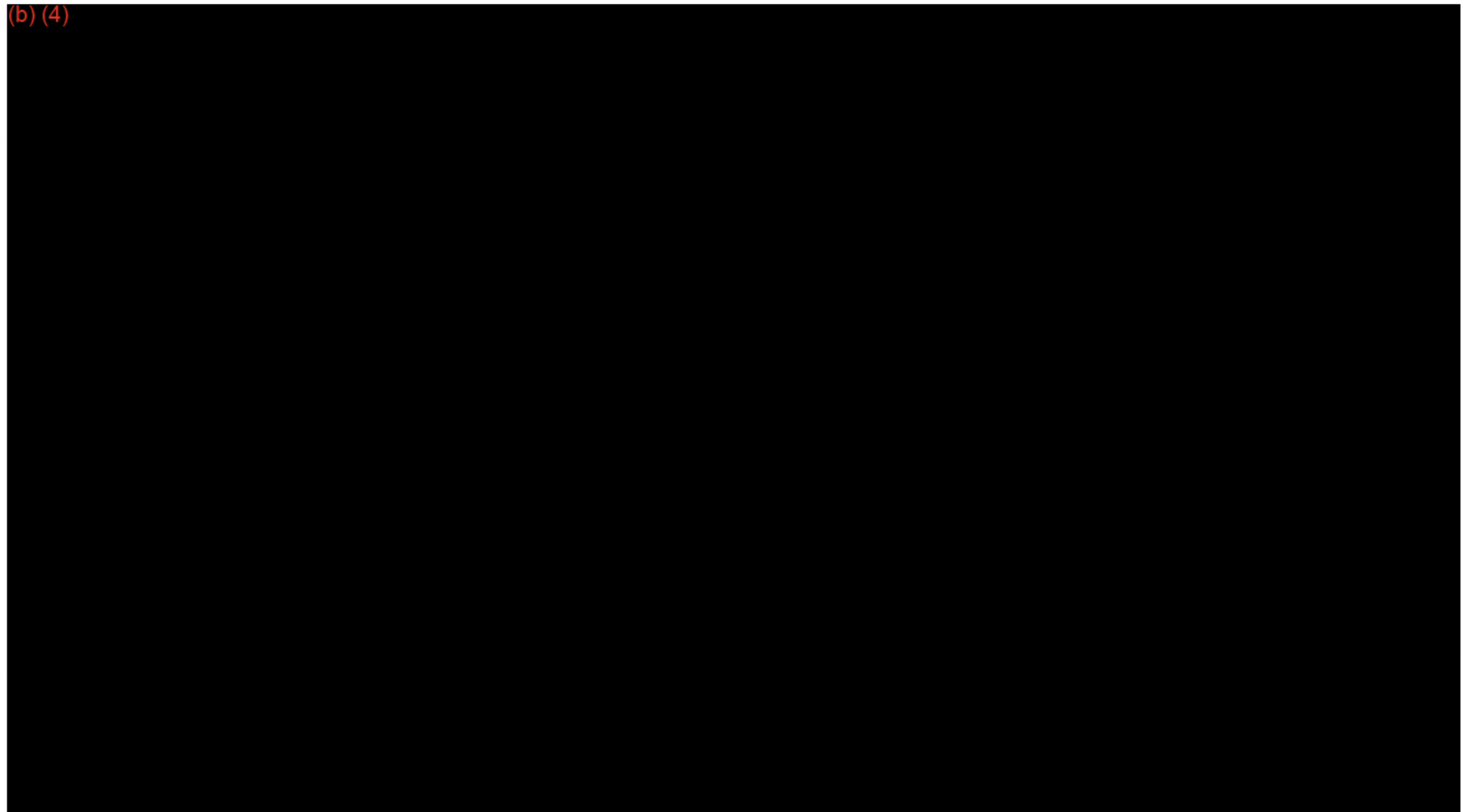
(b) (4)

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Table 31. Table Shell for Secondary Objective 5 – TNP patterns of use among ZYN® users and ZYN® non-users using TNP every day based on weekly use in the prospective observational period.

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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Table 32. Table Shell for Secondary Objective 5 – TNP patterns of use among ZYN® users and ZYN® non-users using TNP every day or some days based on weekly use in the prospective observational period.

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

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Table 33. Table Shell for Secondary Objective 5 – TNP patterns of use among ZYN® users, percent of ZYN® users using ZYN® with other TNP.

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Table 34. Table Shell for Secondary Objective 5 – TNP patterns of use among ZYN® users and ZYN® non-users, intention to quit TNP during the prospective observational period based on the Motivation to Stop Scale (MTSS).

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

(b) (4)

Table 35. Table Shell for Secondary Objective 5 – TNP patterns of use among ZYN® users during the prospective observational period. Outcomes include percent of days that ZYN® is used, average number of ZYN® pouches used per day, and average number of minutes ZYN® was kept in the mouth.

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

(b) (4)

Table 36. Table Shell for Secondary Objective 5 – Among ZYN® Users, reasons for using ZYN®.

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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STATISTICAL ANALYSIS PLAN
ZYN[®] Patterns of Use

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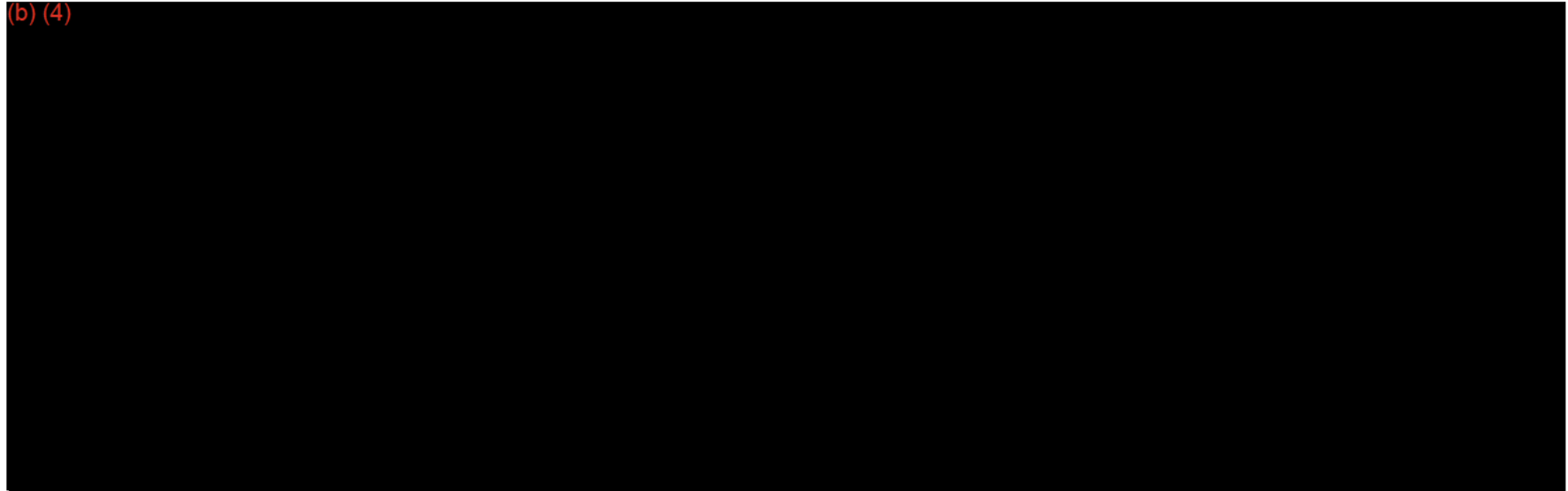
(b) (4)

STATISTICAL ANALYSIS PLAN
ZYN® Patterns of Use

(b) (4)

Table 37. Table Shell for Secondary Objective 6 – Among ZYN® Users and ZYN® Non-users, quitting all TNP use at the end of the prospective observational period, and completely substituting other TNP for ZYN®.

(b) (4)



11. ATTACHMENTS

ZYN® Patterns of Use Study Protocol – November 13, 2017.

ZYN® Patterns of Use Study Retrospective Survey – December 11, 2017.

ZYN® Patterns of Use Study Prospective Survey – December 11, 2017.

[Note: survey item numbers were renumbered for internal use on December 11, 2017].

-LAST PAGE-