Statistical Analysis Plan

Prospective, Non-Randomized, Open-Label, Multi-Center, Single Arm Study of Exchange of Travoprost Intraocular Implant

Protocol Number: IDOS-106-EXCH

Product Name: Travoprost Intraocular Implant, model G2TR-125

Sponsor Name: GLAUKOS CORPORATION
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Statistical Analysis Plan Approval Signatures

The signatures below indicate approval of the Statistical Analysis Plan for this study.

Prepared by: _____ Date

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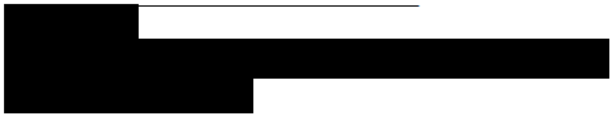

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List of Abbreviations

Abbreviation	Definition
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BSCVA	Best Spectacle Corrected Visual Acuity
CRF	Case Report Form
ECD	Endothelial Cell Density
ETDRS	Early Treatment of Diabetic Retinopathy Study
IOP	Intraocular Pressure
LogMAR	Logarithm of the Minimum Angle of Resolution
MedDRA	Medical Dictionary for Regulatory Activities
MD	Mean Deviation
mmHg	Millimeters of Mercury
OAG	Open-Angle Glaucoma
OHT	Ocular Hypertension
PE	Post-Exchange
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
VA	Visual Acuity
VF	Visual Field
WHO	World Health Organization

Version History

This Statistical Analysis Plan (SAP) for IDOS-106-EXCH is based on the protocol dated 24AUG2020.

1. Introduction

This statistical analysis plan (SAP) describes the statistical methods to analyze all safety data from protocol IDOS-106-EXCH. Any changes to this plan will be reflected as amendments before the database lock and/or documented in the clinical study report. One database lock will occur after all subjects have completed the Month 12 Post-Exchange (PE) visit or have exited the study prior to that time.

Specifications of tables, figures, and data listings are provided in another document.

2. Objectives and Study Design

2.1. Objectives

The study objective is to evaluate the safety of the surgical exchange procedure of the Travoprost Intraocular Implant in subjects with a previously implanted Travoprost Intraocular Implant.

2.2. Endpoints

Safety Endpoints:

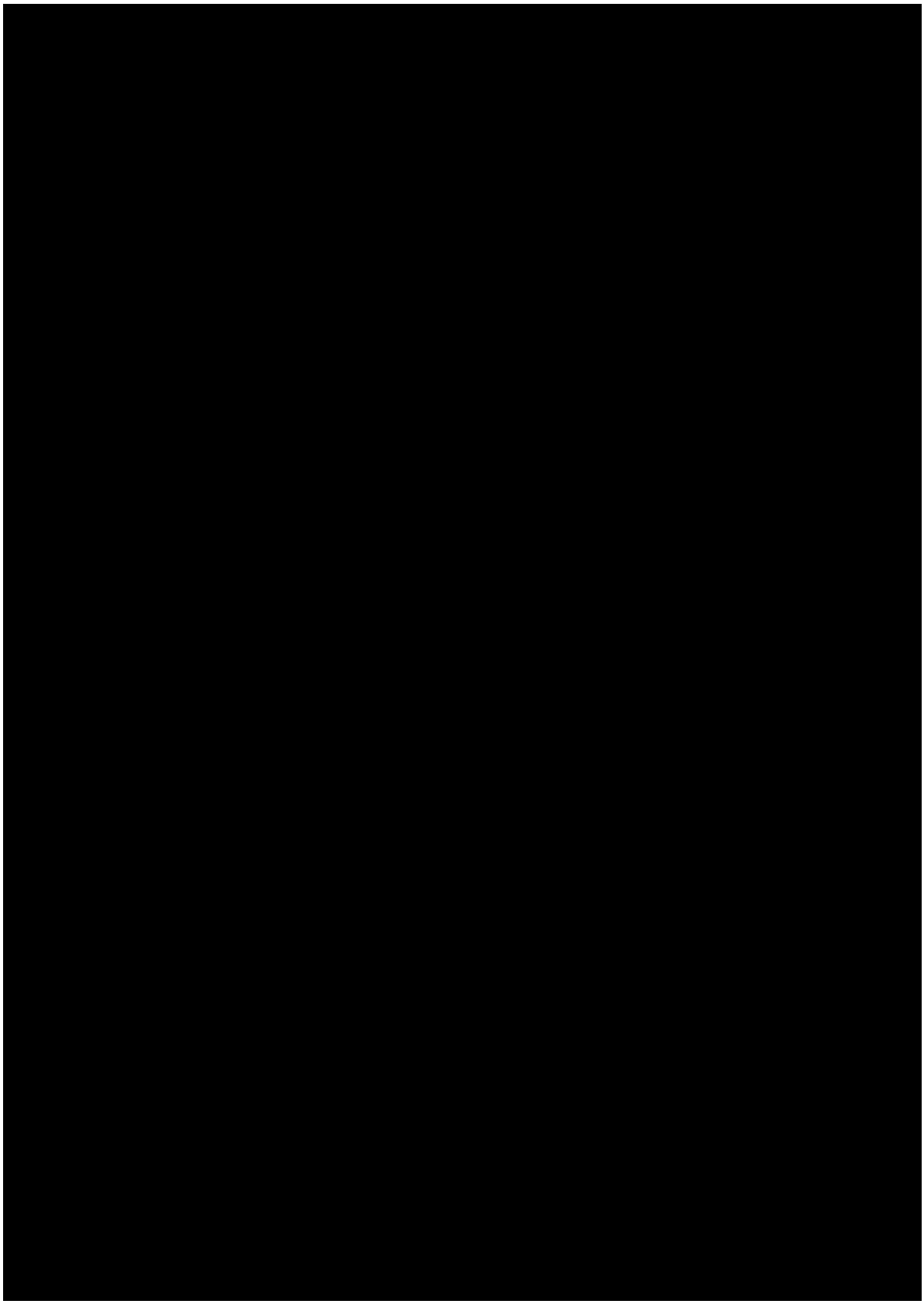
- Intraoperative adverse events
- Postoperative adverse events
- Corrected visual acuity (logMAR score using ETDRS chart)
- Slit-lamp biomicroscopy findings
- Gonioscopy findings
- Specular microscopy findings
- Intraocular Pressure
- Ophthalmoscopy findings
- Visual field evaluation

2.3. Study Design

This is a prospective, non-randomized, open-label, multi-center, single arm clinical trial of the safety of the exchange of the Travoprost Intraocular Implant. Approximately 45 male and female subjects who were previously implanted with the Travoprost Intraocular Implant in the GC-009 study (1st Cycle) were to be enrolled into the study. Subjects will be screened for qualification as per the inclusion/exclusion criteria (refer to Sections **6.2.1** and **6.2.2** of study protocol). Qualified subjects will have the first implant ([redacted] Implant), which was inserted in Study GC-009, exchanged with a second implant (G2TR-125 Implant). Subjects using ocular hypotensive medications at Screening are not required to undergo a medication washout period. Post-treatment management of ocular hypotensive medications is up to the investigator's discretion. Study follow-up will continue until the Month 12 Post-Exchange visit.

The study consists of eight visits: Visit 1 (Screening), Visit 2 (Operative Exchange Day 0), Visit 3 (Day 1 Post-Exchange), Visit 4 (Day 10 Post-Exchange), Visit 5 (Week 4 Post-Exchange), Visit 6 (Month 3 Post-Exchange), Visit 7 (Month 6 Post-Exchange), and Visit 8 (Month 12 Post-Exchange). Subjects will exit the study at the conclusion of the Month 12 Post-Exchange visit.

2.4. Schedule of Visits and Measurements[1]



2.5. Sample Size Determination

[redacted]

3. Analysis Sets

For the purposes of analysis, the following analysis set is defined:

Analysis Set	Description
Safety	All subjects who undergo the exchange procedure.

The safety analysis set will be used for all data tabulations and listings.

4. General Statistical Considerations

Demographic and safety data collected on the case report forms (CRFs) will be displayed in tabulations and data listings. Only data from scheduled visits will be used in tabulations unless otherwise specified. No formal statistical testing will be performed. All data summaries and statistical analyses will be performed using SAS® software, Version 9.4 or higher.

Continuous data will be summarized using the number of observations, mean, standard deviation, median, minimum, and maximum. Continuous data may also be dichotomized, or otherwise split, into clinically meaningful categories and may be further analyzed as categorical data as specified in the individual endpoints.

Categorical data will be summarized using frequency counts and percentages. Unless otherwise stated, subjects with missing visit data will be omitted from both the numerator and denominator of such calculations.

4.1. Definition of Variables

4.1.1. Baseline Measure

The baseline measure is defined as the last non-missing measure prior to the initiation of the investigational product within this study (i.e., second implant at the operative exchange visit).

4.1.2. Change and Percent Change from Baseline

The change from baseline and the percent change from baseline values are calculated as

- Change from baseline value = follow-up visit value – baseline value.
- Percent Change from baseline value = (change from baseline value / baseline value) * 100.

4.1.3. Study Days

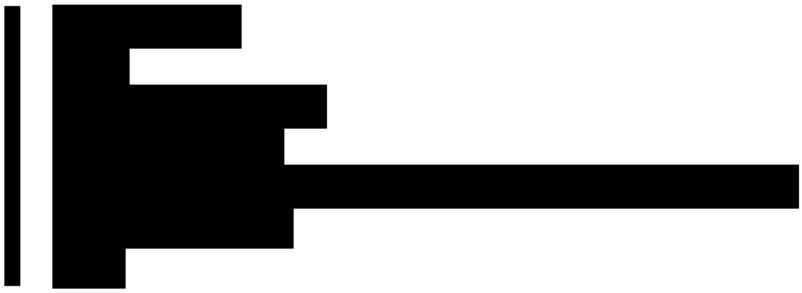
The number of study days is defined relative to the Operative Exchange visit, starting with the Operative visit as study day 1. For each date following the Operative visit, the study day value increases by 1. For each date prior to the Operative visit, the study day value decreases by 1, with the date preceding the Operative visit as study day -1. Note that the operative visit is sometimes referred to as the Operative Exchange Day 0 visit in the protocol. In the statistical analysis plan and summaries, this visit will be considered day 1.

5. Demographic and Baseline Characteristic Analyses

5.1. Subject Disposition

The number and percentage of subjects who were screened, screened but not enrolled (i.e., screen failures), and enrolled will be provided. A subject is considered enrolled at the time the subject undergoes surgery. Reason(s) for screen failure will also be presented in a table and subject listing.

Subject disposition will be summarized for all enrolled subjects. The summary will include the number and percentage of subjects who completed the study and the number and percentage of subjects who exited early (with reasons for study exit) prior to the Month 12 PE examination. The reasons for early study exit include:



Subject disposition and exit status will also be listed by subject.

5.2. Protocol Deviations

Protocol deviations will be captured by the site and reviewed by a medical monitor during the study. Classification of major deviations will be decided by the study team prior to the database lock. A summary of protocol deviations will be tabulated for the safety analysis set. A listing of all protocol deviations will be provided.

5.3. Demographic and Baseline Characteristics

Subject demographics and baseline characteristics will be tabulated for the safety analysis set. Demographic variables include age, sex, race, and ethnicity. Age will be calculated for each subject by (Informed Consent Date – Date of Birth) ÷ 365.25 and rounded down to the nearest integer.

The following baseline characteristics will be summarized for the study eye:

- Type of Disease (OAG or OHT .)
- IOP (mmHg)
- Best Spectacle Corrected Visual Acuity (BSCVA) - LogMAR
- Visual Field Mean Deviation (dB)
- Vertical Cup-to-Disc Ratio
- Corneal Thickness (µm)

[redacted]

Demographic and baseline characteristic data will be listed.

5.4. Medical and Surgical History

All medical and surgical history will be coded to the Medical Dictionary for Regulatory Activities (MedDRA) nomenclature, [redacted]. Ocular and non-ocular medical and surgical history will be tabulated by System Organ Class (SOC) and preferred term (PT). The ocular history tabulation will present summaries for the study eye, non-study eye, and overall groups. Subjects with more than one medical history within a given SOC or PT will only be counted once within that SOC or PT. Ocular and non-ocular medical and surgical history will be listed by subject.

5.5. Prior and Concomitant Medications

Prior medications are defined as those medications taken within 30 days prior to the start of Screening with a stop date prior to study drug administration. Concomitant medications are defined as those medications taken (1) prior to study drug administration and continuing for any period of time following the first administration of study drug or (2) at any time following the first administration of study drug.

Medications will be coded using the World Health Organization (WHO) Drug Dictionary [redacted] and will be summarized to the anatomical therapeutic chemical (ATC) class and preferred name. Prior and concomitant ocular medications will be tabulated separately. The tabulations will present summaries for the study eye, non-study eye, and overall groups. Subjects will be counted only once under each ATC class or preferred name for which they have at least one medication. All prior and concomitant medications will be listed.

5.6. Concurrent Ocular Procedures

Concurrent ocular procedures are defined as any ocular procedures that occurred in the study eye on or after the date of the exchange surgery. Ocular procedures will be coded using the MedDRA nomenclature, [redacted]. Ocular procedures will be tabulated by SOC and PT. Subjects with more than one ocular procedure within a given SOC or PT will only be counted once within that SOC or PT. All concurrent ocular procedures will be listed.

6. Efficacy Analyses

6.1. Primary Endpoint Efficacy Analysis

There are no primary efficacy endpoints in this study.

6.2. Secondary Endpoint Efficacy Analysis

There are no secondary efficacy endpoints in this study.

6.3. Exploratory Endpoint Efficacy Analysis

There are no exploratory efficacy endpoints in this study.

7. Safety Analyses

All safety analyses will be based on the safety analysis set and will be described in more detail in the following sections.

7.1.1. Extent of Exposure

Summaries of the extent of exposure to study treatment, which include the number of participants exposed and descriptive statistics of the duration of exposure in study days, will be provided for the study. Extent of exposure to study treatment in days will be calculated as date of study exit – date of exchange surgery + 1. If the date of study exit is missing for a subject with early study exit, the date of the last recorded visit will be used for calculations. A listing of extent of exposure will be provided.

7.1.2. Adverse Events

Adverse events (AEs) will be coded to the MedDRA nomenclature, [redacted]. Treatment Emergent Adverse Events (TEAEs) are defined as AEs that occur after the initiation of the exchange surgery at Visit 2 (Operative Exchange Day 0).

A summary of the number and percentage of subjects with TEAEs will be provided for the safety analysis set. The summary will include study eye TEAEs, non-ocular or non-study eye TEAEs, treatment-related TEAEs, TEAEs by maximum severity, TEAEs resulting in study discontinuation, serious TEAEs, and deaths.

The number and percentage of subjects with TEAEs will be tabulated by SOC and PT for:

- Ocular TEAEs
- Non-ocular TEAEs
- Ocular TEAEs related to study treatment
- Non-ocular TEAEs related to study treatment
- Ocular TEAEs by maximum severity
- Non-ocular TEAEs by maximum severity
- Ocular serious TEAEs
- Non-ocular serious TEAEs

All tabulations of ocular TEAEs will contain summaries for the study eye, non-study eye, and overall groups.

All AEs will be presented in a listing by subject. Separate listings for intraoperative AEs, serious adverse events (SAEs) including deaths, AEs leading to early study exit, and AEs leading to removal of implant will also be presented.

Relationship to study treatment is defined as the possibility that the study treatment caused the event and is described in the study protocol. The relationship to study treatment categories utilized on the CRF are definitely unrelated, unlikely related, possibly related, probably related, and definitely related. For all tabulations, the categories of possibly related, probably related, and definitely related will be classified as related and only related AEs will be presented. AEs

with missing relationships are counted as related. Subjects experiencing more than one treatment related AE within a given SOC or PT will be counted once within that SOC or PT.

Severity is a measure of intensity and is graded on a 3-point scale as outlined in the study protocol. AEs will be rated as either mild, moderate, or severe. AEs with missing severities are counted as severe. For all tabulations, subjects experiencing more than one AE within a given SOC or PT will be counted once within that SOC or PT at the maximum severity.

7.1.3. Additional Safety Assessments

Additional safety measures will be summarized for the Safety analysis set. Only data in the study eye will be presented in tabulations. Data may be tabulated by visit and/or for the overall study (i.e. subjects with at least one finding during the study) as indicated. Summaries for the overall study will include data from unscheduled visits.

The criteria for clinical significance varies by measure. [redacted]

7.1.3.1. Corrected Visual Acuity

[redacted]

The actual and change from baseline in BSCVA will be summarized by visit. The summary will include continuous descriptive statistics on the number of letters read correctly. In addition, the number and percentage of subjects with a decrease of greater than or equal to 15 letters (3 lines) will be summarized by visit.

A visual acuity subject listing will be provided for all visual acuity data including pinhole VA.

7.1.3.2. Slit Lamp Examinations

Slit lamp measures collected on the CRF include corneal edema, corneal opacity, epithelium, endothelium, guttata, anterior chamber depth, anterior chamber cells, anterior chamber flare, pupil, iris, conjunctival hyperemia, and iris color change. All slit lamp measures, excluding conjunctival hyperemia and iris color change, are collected at Screening and each postoperative visit. Conjunctival hyperemia and iris color change are collected at all postoperative visit except for the Day 1 PE visit.

For each measure, the number and percentage of subjects will be summarized by visit for each severity grade/category.

[redacted]

Conjunctival hyperemia will be summarized by visit. [redacted]

All slit lamp data will be listed by subject. An additional slit lamp listing for subjects with findings will be presented. [redacted] Other slit lamp findings will be provided in a separate listing.

7.1.3.3. Lens Findings

Lens measures are collected at Screening and each postoperative visit. Lens measures include lens status, posterior capsule opacification, nuclear lens opacity, cortical lens opacity, and posterior subcapsular lens opacity.

For each measure, the number and percentage of subjects will be summarized by visit for each severity grade/category.

[redacted]

All lens data will be listed by subject. [redacted]

Other lens findings will be provided in a separate listing. Lens status (phakic or pseudophakic) will be listed and not tabulated.

7.1.3.4. Ophthalmoscopy Examinations

Dilated fundus assessments are evaluated at the Screening and Month 12 PE visits. Either undilated or dilated fundus assessments may be evaluated at the Week 4 PE, Month 3 PE, and Month 6 PE visits. Dilated and undilated fundus measures (Macula, Vessels, Periphery, Vitreous, Other) will be tabulated by visit for each severity grade. [redacted]

[redacted]

Nerve abnormality findings are collected at the Screening, Week 4 PE, Month 3 PE, Month 6 PE, and Month 12 PE visits. The number and percentage of subjects with findings (Segmental Loss of Neuroretinal Rim, Nerve Fiber Layer Loss, Disc Hemorrhage, Other) will be tabulated by visit. [redacted] All nerve abnormality data will be listed by subject. [redacted]

Vertical cup-to-disc ratio is evaluated at the Screening, Month 3 PE, and Month 12 PE visits. The actual and change from baseline in vertical cup-to-disc ratio will be summarized as a continuous variable by visit. [redacted]

[redacted] A listing of vertical cup-to-disc ratio and change in vertical cup-to-disc ratio will be provided by subject.

7.1.3.5. Gonioscopy

Gonioscopy assessments are performed at the Screening, Week 4 PE, Month 3 PE, Month 6 PE and Month 12 PE visits. Gonioscopy findings include goniosynechiae, angle rubeosis, and other angle abnormalities. [redacted]

7.1.3.6. Implant Visibility

[redacted]

7.1.3.7. Visual Field

Visual field mean deviation (MD) is collected at Screening and the Month 12 PE visit. The actual and change from baseline in visual field MD will be summarized as a continuous variable by visit.

A listing will be presented for all visual field MD data.

7.1.3.8. Specular Microscopy

Specular microscopy findings are collected at the Screening, Month 3 PE, and Month 12 PE visits. Endothelial cell density (ECD), percent hexagonality, and the coefficient of variation (COV) will be assessed from calibrated specular microscope images. The actual, change from baseline, and percent change from baseline in ECD (cells/mm^2) will be summarized as a continuous variable by visit for the central location. In addition, the number and percentage of subjects with central ECD loss will be tabulated by visit and for the overall study (i.e., based on the minimum change from baseline across all postoperative visits) for the following categories:

[redacted]

The actual and change from baseline in percent hexagonality (%) and COV (%) will be summarized continuously by visit for the central location.

A listing presenting all ECD data will be provided.

7.1.3.9. Corneal Pachymetry

Corneal pachymetry assessments are performed at the Screening, Month 3 PE, and Month 12 PE visits. The actual and change from baseline in central corneal thickness (µm) via pachymetry will be summarized by visit as a continuous variable.

All pachymetry data will be presented in a listing.

7.1.3.10. Intraocular Pressure

IOP is assessed for safety and is measured at Screening and all postoperative visits. At Screening, IOP may be collected at any time of the day. At the remaining examinations, IOP must be measured at the same time as Screening ± 60 minutes.

The actual and change from baseline in IOP (mmHg) will be summarized by visit as a continuous variable. [redacted]

A subject listing presenting all IOP data will be provided.

8. Other Analyses

Other Analyses will be summarized as outlined in the subsequent sections.

[redacted]

8.1.2. Operative and Surgical Analyses

Operative and surgical parameters will be summarized for the Operative Exchange visit. [redacted] All operative and surgical parameters will be presented in a subject listing.

8.1.3. Subgroup Analyses

No subgroup analyses are planned.

9. Interim Analysis

No interim analyses will be performed.

10. Changes to Protocol-planned Analyses

No changes to the protocol-planned analyses have occurred.

11. Supporting Documentation

11.1. Appendix: Data Derivation Rules

11.1.1. Corrected Visual Acuity Derivation

[redacted]

11.1.2. IOP Derivation

[redacted]

12. References

[redacted]