TheraPanacea
% Bhairavi Ajachandra
QA/RA Manager
7 bis boulevard Bourdon
Paris, 75004
FRANCE

December 22, 2023

Re: K232479
Trade/Device Name: ART-Plan
Regulation Number: 21 CFR 892.5050
Regulation Name: Medical Charged-Particle Radiation Therapy System
Regulatory Class: Class II
Product Code: MUJ
Dated: November 20, 2023
Received: November 20, 2023

Dear Bhairavi Ajachandra:

We have reviewed your section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (the Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database available at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Additional information about changes that may require a new premarket notification are provided in the FDA guidance documents entitled "Deciding When to Submit a 510(k) for a Change to an Existing Device" (https://www.fda.gov/media/99812/download) and "Deciding When to Submit a 510(k) for a Software Change to an Existing Device" (https://www.fda.gov/media/99785/download).

Your device is also subject to, among other requirements, the Quality System (QS) regulation (21 CFR Part 820), which includes, but is not limited to, 21 CFR 820.30, Design controls; 21 CFR 820.90, Nonconforming

product; and 21 CFR 820.100, Corrective and preventive action. Please note that regardless of whether a change requires premarket review, the QS regulation requires device manufacturers to review and approve changes to device design and production (21 CFR 820.30 and 21 CFR 820.70) and document changes and approvals in the device master record (21 CFR 820.181).

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR Part 803) for devices or postmarketing safety reporting (21 CFR Part 4, Subpart B) for combination products (see https://www.fda.gov/combination-products/guidance-regulatory-information/postmarketing-safety-reporting-combination-products); good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820) for devices or current good manufacturing practices (21 CFR Part 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR Parts 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR 807.97). For questions regarding the reporting of adverse events under the MDR regulation (21 CFR Part 803), please go to https://www.fda.gov/medical-devices/medical-device-safety/medical-device-reporting-mdr-how-report-medical-device-problems.

For comprehensive regulatory information about medical devices and radiation-emitting products, including information about labeling regulations, please see Device Advice (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance) and CDRH Learn (https://www.fda.gov/training-and-continuing-education/cdrh-learn). Additionally, you may contact the Division of Industry and Consumer Education (DICE) to ask a question about a specific regulatory topic. See the DICE website (https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/contact-us-division-industry-and-consumer-education-dice) for more information or contact DICE by email (DICE@fda.hhs.gov) or phone (1-800-638-2041 or 301-796-7100).

Sincerely,

Lora D. Weidner, Ph.D.
Assistant Director
Radiation Therapy Team
DHT8C: Division of Radiological Imaging
and Radiation Therapy Devices
OHT8: Office of Radiological Health
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Indications for Use

Form Approved: OMB No. 0910-0120
Expiration Date: 06/30/2023
See PRA Statement below.

510(k) Number *(if known)*
K232479

Device Name
ART-Plan

Indications for Use *(Describe)*

ART-Plan's indicated target population is cancer patients for whom radiotherapy treatment has been prescribed. In this population, any patient for whom relevant modality imaging data is available.

ART-Plan is not intended for patients less than 18 years of age.

The indicated users are trained medical professionals including, but not limited to, radiotherapists, radiation oncologists, medical physicists, dosimetrists and medical professionals involved in the radiation therapy process.

The indicated use environments are, but not limited to, hospitals, clinics and any health facility involved in radiation therapy.

Type of Use *(Select one or both, as applicable)*

☒ Prescription Use (Part 21 CFR 801 Subpart D) ☐ Over-The-Counter Use (21 CFR 801 Subpart C)

CONTINUE ON A SEPARATE PAGE IF NEEDED.

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K232479

TheraPanacea SAS
Traditional 510(k)
ART-Plan

510(k) Summary

This 510(k) Summary is submitted in accordance with 21 CFR Part 807, Section 807.92.

Level of documentation:

Enhanced

Submitter's Name:

TheraPanacea SAS

Submitter's Address:

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France

Telephone: +33 9 62 52 78 19

Establishment Registration Number:

3019834893

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Date Prepared:

10 Aug 2023

Below summaries the Device Classification Information regarding the TheraPanacea ART-Plan:

Primary Product Code:

Regulation Number	Device	Device Class	Product Code	Classification Panel
892.5050	Medical charged-particle radiation therapy system	Class II	MUJ	Radiology

Device Trade Name:

ART-Plan

Device Common Name:

ART-Plan

TheraPanacea SAS
Traditional 510(k)
ART-Plan

Intended Use:

ART-Plan is a software intended to be used by trained clinicians who are familiar with radiation therapy, such as medical physicists, medical dosimetrists and radiation oncologists. The software consists of different applications, each used for specific purposes at a different phase of radiation treatment planning.

ART-Plan offers the following tools to aid in the workflow of radiotherapy treatment:

- Multi-modal visualization and rigid- and deformable registration of anatomical and functional images such as CT, MR, PET-CT, 4D-CT, CBCT and synthetic-CT generated from CBCT
- Display of fused and non-fused images to facilitate the comparison and delineation of image data by the user
- Manual generation, modification and semi-automatic generation of contours for the regions of interest
- Automatic generation of contours for organs at risk and healthy lymph nodes, based on medical practices, on medical images such as CT and MR images
- Generation of synthetic-CT from MR images for supported anatomies
- Generation of synthetic-CT from CBCT images for supported anatomies
- Dose computation on CT and/or synthetic-CT images for external beam irradiation with photon beams
- Assisted CBCT-based off-line adaptation decision-making for supported anatomies

The device is intended to be used in a radiation therapy clinical setting, by trained professionals only.

Indications for Use:

ART-Plan's indicated target population is cancer patients for whom radiotherapy treatment has been prescribed. In this population, any patient for whom relevant modality imaging data is available.

ART-Plan is not intended for patients less than 18 years of age.

The indicated users are trained medical professionals including, but not limited to, radiotherapists, radiation oncologists, medical physicists, dosimetrists and medical professionals involved in the radiation therapy process.

The indicated use environments include, but are not limited to, hospitals, clinics and any health facility involved in radiation therapy.

Summary of Substantial Equivalence:

The following predicate devices have been chosen that the ART-Plan can claim equivalence with and these are detailed below in Table 1. Summary of Substantial Equivalence.

General Comparison

	General Information					
Property	***Proposed Device*** **ART-Plan v2.1.0**	***Primary Predicate*** **Ethos Treatment Management, 2.1; Ethos Treatment Planning, 1.1**	***Reference device*** **ART-Plan v1.10.1**	***Reference device*** **ECLIPSE WITH AAA**	***Reference device*** **Eclipse Treatment Planning System**	**Comment**
Common Name	System, Planning, Radiation Therapy Treatment	accelerator, linear, medical	Radiological image processing software for radiation therapy	System, Planning, Radiation Therapy Treatment	System, Planning, Radiation Therapy Treatment	The proposed device shares the same common name ”System, Planning, Radiation Therapy Treatment” with the primary predicate, especially Ethos Treatment Planning, 1.1 (that has “MUJ” as a product code in its 510(k) summary) and with some of the reference devices.
Device Manufacturer	TheraPanacea SAS	Varian Medical Systems, Inc	TheraPanacea SAS	Varian Medical Systems (now Varian Medical Systems, Inc)	Varian Medical Systems, Inc	N/A
510k	N/A	K212294	K230023	K041403	K102011	N/A
Device Classification	II	II	II	II	II	The proposed device, primary predicate and reference devices have identical device classification.
Primary Product Code	MUJ	IYE, MUJ	QKB	MUJ	MUJ	The primary product code is MUJ for “System, Planning, Radiation Therapy Treatment” as it is a software used in the planning of radiotherapy treatment like the primary predicate, especially Ethos Treatment Planning, 1.1 (that has “MUJ” as a product code in its 510(k) summary) and some reference devices use it as their primary or secondary code

Secondary Product Code	QKB, LLZ	-	LLZ, MUJ	-	LHN	As secondary product code: - QKB (Radiological image processing software for radiation therapy) has been included as the software uses AI algorithms and is intended for radiation therapy. It is also the primary code of the reference device ART-Plan v1.10.1 of which ART-Plan 2.1.0 is an update; - LLZ (System, Image Processing, Radiological) has been included as the software is used in image processing and it is also the subsequent code of the reference device ART-Plan v1.10.1 of which ART-Plan 2.1.0 is an update.
Target Population	ART-Plan's indicated target population is cancer patients for whom radiotherapy treatment has been prescribed. In this population, any patient for whom relevant modality imaging data is available.	The patient target groups are the patients for whom radiation therapy is indicated.	ART-Plan's indicated target population is cancer patients for whom radiotherapy treatment has been prescribed. In this population, any patient for whom relevant modality imaging data is available.	Not stated	Any patients with malignant or benign diseases	The proposed device and the primary predicate have identical target populations.
Environment	Hospital	Hospital	Hospital	Hospital	Hospital	The proposed device, primary predicate and reference devices have identical target environments.
Intended Use/ Indication for Use	**Intended Use** ART-Plan is a software intended to be used by trained clinicians who are familiar with radiation therapy, such as medical physicists, medical dosimetrists and	**Intended Use** Ethos Treatment Management is used to manage and monitor radiation therapy treatment plans and sessions; it is intended to be used	**Intended Use** ART-Plan is a software for multi-modal visualization, contouring and processing of 3D images of cancer patients for whom	**Intended Use** The Varian Eclipse device is a treatment planning system used for diagnostic image analysis, contouring and segmentation, geometrical	**Intended use** Not available in the summary: **Indication for use** The Eclipse Treatment Planning System (Eclipse TPS) is used to plan radiotherapy	The intended use and indications for use of the proposed device, ART-Plan v2.1.0 and the primary predicate (especially Ethos Treatment Planning, 1.1) are similar as they are both softwares intended to be used in the planning of radiotherapy treatment[1]:

[1] Information found on the predicate current or previous 510(k) summaries, labelling and its manufacturer's (Varian Medical Systems, Inc) website.

	radiation oncologists. The software consists of different applications, each used for specific purposes at a different phase of radiation treatment planning. ART-Plan offers the following tools to aid in the workflow of radiotherapy treatment: Multi-modal visualization and rigid- and deformable registration of anatomical and functional images such as CT, MR, PET-CT, 4D-CT, CBCT and synthetic-CT generated from CBCT Display of fused and non-fused images to facilitate the comparison and delineation of image data by the user Manual generation, modification and semi-automatic generation of contours for the regions of interest	with a treatment planning system. Ethos Treatment Planning is used to generate and modify radiation therapy treatment plans. **Indications for Use** Ethos Treatment Management is indicated for use in managing and monitoring treatment plans and sessions. Ethos Treatment Planning is indicated for use in generating and modifying radiation therapy treatment plans.	radiotherapy treatment has been prescribed. It allows the user to view, create and modify contours for the regions of interest. It also allows to generate automatically, and based on medical practices, the contours for the organs at risk and healthy lymph nodes and to register combinations of anatomical and functional images. Contours and images require verifications, potential modifications, and subsequently the validation of a trained user with professional qualifications in anatomy and radiotherapy before their export to a Treatment Planning System. ART-Plan offers the following visualization, contouring and manipulation tools to aid in the preparation of radiotherapy treatment: - Multi-modal visualization and rigid- and deformable registration of anatomical and functional images	planning, photon and electron dose calculation and plan review. **Indication for use** The Varian Eclipse device is used to plan photon and electron radiation therapy treatments employing linear accelerators and other similar teletherapy devices with x-ray energies from 1-50 MV, as well as Cobalt-60, and electron energies from 1-50 MeV. Eclipse will plan the 3D radiotherapy treatment approaches to combined modality plans, coplanar and non-coplanar fields, static and ARC fields, beam modifiers, and beam intensity modulators. Eclipse also includes tools for treatment preparation (diagnostic image and analysis, contouring and segmentation) and plan review.	treatments for patients with malignant or benign diseases. Eclipse TPS is used to plan external beam irradiation with photon, electron and proton beamA, as well as for internal irradiation (brachytherapy) treatments. In addition, the Eclipse Proton Eye algorithm is specifically indicated for planning proton treatment of neoplasms of the eye.	they allow multi-modal visualisation rigid rigid- and deformable registration for the same modalities of images (CT, MR and PET) they allow displaying fused and non-fused images to facilitate the comparison and delineation of image data by the user they allow manual generation, modification and semi-automatic generation of contours for the regions of interest they allow automatic segmentation on medical images using AI algorithms they allow generation of synthetic-CT from CBCT images they allow dose computation on CT and/or synthetic-CT images for external beam irradiation with photon beams they allow assisted CBCT-based off-line adaptation decision-making for supported anatomies they allow the import, manipulation, visualisation, generation and the export of DICOM images The intended use for the proposed device has been adapted to provide a more specific description of the proposed device but does not represent a new intended use, except for the additional modality for the same claim as compared to the primary predicate as:

	Automatic generation of contours for organs at risk and healthy lymph nodes, based on medical practices, on medical images such as CT and MR images Generation of synthetic-CT from MR images for supported anatomies Generation of synthetic-CT from CBCT images for supported anatomies Dose computation on CT and/or synthetic-CT images for external beam irradiation with photon beams Assisted CBCT-based off-line adaptation decision-making for supported anatomies The device is intended to be used in a radiation therapy clinical setting, by trained professionals only. **Indications for Use** ART-Plan's indicated target		such as CT, MR, PET-CT, 4D-CT and CBCT - Display of fused and non-fused images to facilitate the comparison and delineation of image data by the user - Manual modification and semi-automatic generation of contours for the regions of interest - Automatic generation of contours for organs at risk and healthy lymph nodes, based on medical practices, on medical images such as CT and MR images. - Generation of pseudo-CT for supported anatomies The device is intended to be used in a radiation therapy clinical setting, by trained professionals only. **Indications for Use** ART-Plan is indicated for cancer patients for whom radiation treatment has been planned. It is intended to be used by trained medical professionals including, but not limited to, radiologists,			- it can generate synthetic CT from CBCT and MR images whereas it is not possible with Ethos Treatment Planning, 1.1 to do so with MR images. This does not represent an additional claim as the technological characteristics are the same and it does not raise different questions of safety and effectiveness. Also, this feature is covered by the reference device ART-Plan v1.10.1, which is the previous version cleared of the proposed device ART-Plan v2.1.0.

	population is cancer patients for whom radiotherapy treatment has been prescribed. In this population, any patient for whom relevant modality imaging data is available. ART-Plan is not intended for patients less than 18 years of age. The indicated users are trained medical professionals including, but not limited to, radiotherapists, radiation oncologists, medical physicists, dosimetrists and medical professionals involved in the radiation therapy process. The indicated use environments include, but are not limited to, hospitals, clinics and any health facility involved in radiation therapy.		radiation oncologists, dosimetrists, and medical physicists. ART-Plan is a software application intended to display and visualize 3D multi-modal medical image data. The user may import, define, display, transform and store DICOM 3.0 compliant datasets (including regions of interest structures). These images, contours and objects can subsequently be exported/distributed within the system, across computer networks and/or to radiation treatment planning systems. Supported modalities include CT, PET-CT, CBCT, 4D-CT and MR images. ART-Plan supports AI-based contouring on CT and MR images and offers semi-automatic and manual tools for segmentation. To help the user assess changes in image data and to obtain combined multi-modal image information, ART-Plan allows the registration of anatomical and			

			functional images and display of fused and non-fused images to facilitate the comparison of patient image data by the user. With ART-Plan, users are also able to generate, visualize, evaluate and modify pseudo-CT from MRI images. .			

System Information Comparison

	System Information					
Property	***Proposed Device*** **ART-Plan v2.1.0**	***Primary Predicate*** **Ethos Treatment Management, 2.1; Ethos Treatment Planning, 1.1**	***Reference device*** **ART-Plan v1.10.1**	***Reference device*** **ECLIPSE WITH AAA**	***Reference device*** **Eclipse Treatment Planning System**	**Comment**
Method of Use	Standalone software application accessed via a compliant browser (Chrome, Mozilla Firefox and Edge) on a personal computer, tablet or phone (In case of connection to the platform with a screen of a phone or a tablet, the user must choose the option for the desktop site of his communication device. The platform is optimally used with 17 inches and up screen. Facilitates display and visualization of data by user.	Standalone software device	Standalone software application accessed via a compliant browser (Chrome or Mozilla Firefox) on a personal computer, tablet or phone (In case of connection to the platform with a screen of a phone or a tablet, the user must choose the option for the desktop site of his communication device. The platform is optimally used with 17 inches and up screen. Facilitates display and visualization of data by user.	Computer based software device	Computer based software device	The proposed device and the primary predicate are both standalone software. More details have been found on the reference device ART-Plan v1.10.1 which has identical methods of use than the proposed device. An improvement has been introduced with ART-plan v2.1.0 as it can be also used on Edge browser.
Data Visualization / Graphical Interface	Yes	Yes	Yes	Yes	Yes	The proposed device, the primary predicates and all references devices have a data visualisation and graphical interface
Synthetic CT	Generation of CT density image series out of multiple MR-image series and CBCT images	Generation of CT density image series out of CBCT images	Generation of CT density image series out of multiple MR-image series	N/A	N/A	The proposed device and primary predicate can generate synthetic-CT from CBCT image. The proposed device can generate synthetic CT from CBCT and MR images whereas it is not possible with

						the primary predicate to do so with MR images. This does not represent an additional claim as the technological characteristics are the same and it does not raise different questions of safety and effectiveness. Also, this feature is covered by the reference device ART-Plan v1.10.1, which is the previous version cleared of the proposed device ART-Plan v2.1.0.
Dose computation	Dose computation on CT and/or synthetic-CT images for external beam irradiation with photon beams	Dose calculation with AAA dose calculation model and Acuros XB dose calculation algorithm on CT and / or synthetic CT images	N/A	The AAA dose calculation model is a 3D convolution/superposition algorithm that models primary photons, photons scattered in the medium, contamination electrons and transport electrons near tissue heterogeneities. The AAA dose calculation model is comprised of two main components, one being the configuration algorithm and the other one the actual dose calculation algorithm.	AcurosXB dose calculation algorithm	The proposed device, the primary predicate and some reference devices ECLIPSE WITH AAA and Eclipse Treatment Planning System can perform dose computation.
Off-line adaptation decision-making	Assisted CBCT-based off-line adaptation decision-making for supported anatomies	Ethos Treatment Management allows the physician to do initial planning, review and approve candidate plans, and monitor ongoing treatments. Support for adaptive radiotherapy	N/A	N/A	N/A	The proposed device and the primary predicate can assist off-line adaptation decision-making.

		treatment planning and automated plan generation				
Supported Modalities	**Registration**: Static and gated CT, MR, PET (via the registration of the CT of said PET), 4D-CT, CBCT and synthetic-CT generated from CBCT **Segmentation**: CT (injected or not), MR images, DICOM RTSTRUCT, synthetic-CT from CBCT	**Registration:** CT (including synthetic CT from CBCT), MR and PET **Segmentation:** CT and synthetic CT from CBCT	**Registration**: Static and gated CT (including 4D-CT and CBCT), MR, PET (via the registration of the CT of said PET) **Segmentation**: CT (injected or not), MR images, DICOM RTSTRUCT	**Segmentation:** Eclipse also includes tools for treatment preparation (diagnostic image and analysis, contouring and segmentation) and plan review.	**Registration:** CT/MR/PET Image Registration 4D image display (registration of time yes yes series of 3D images) **Segmentation:** Geometrical shapes, Manual editing and manipulation tools, Automatic /semi-automatic tools, Automatic/semi-automatic on-demand and post-processing tools for individual organs/structures, Automatic on-demand and pre-processing tools for multiple organs/structures, 3D Autornargin, Logical operators	The proposed device, the primary predicate and most of the reference devices propose both registration and segmentation on medical images of different modalities.
Data Export	Distribution of DICOM compliant Images into other DICOM compliant systems.	ARIA RadOnc integration, DICOM RT, other image formats, eclipse scripting API (ESAPI) read only access, eclipse scripting API (ESAPI) write access, Eclipse automation, Export field coordinates to laser system, basic	Distribution of DICOM compliant Images into other DICOM compliant systems.	DICOM including RT objects, MDC shaper files, blocks and compensator data to Par Scientific, plan and dose data to picker AcQSim, integrated with Varis verification, ASCIIfile to laser system, Varian CadPlan plus 6.0	VARiS/Vision database integration, DICOM RT/3.0, other image formats, export field coordinates to laser system	The proposed device, the primary predicate and reference devices have identical data export capabilities with DICOM format.

		RT prescription information available				
Compatibility	Compatible with data from any DICOM compliant scanners for the applicable modalities.	ARIA RadOnc integration, DICOM RT, other image formats, electromagnetic digitizer, eclipse scripting API (ESAPI) read only access, eclipse scripting API (ESAPI) write access, eclipse automation, Basic RT prescription information available	Compatible with data from any DICOM compliant scanners for the applicable modalities.	DICOM including RT objects, CART format, TIFF format, CMP format, Configurable pure pixel data, PortalVision MArk 1 & 2, Varian CT option, Electromagnetic Digitilizer, Film scanner	VARIs/Vision database integration, DICOM RT/3.0, other image formats, Electromagnetic digitizer, film scanner	The proposed device, the primary predicate and reference devices have identical compatibility (DICOM format)

Technical Information Comparison

		Technical Information				
Property	***Proposed Device*** **ART-Plan v2.1.0**	***Primary Predicate*** **Ethos Treatment Management, 2.1; Ethos Treatment Planning, 1.1**	***Reference device*** **ART-Plan v1.10.1**	***Reference device*** **ECLIPSE WITH AAA**	***Reference device*** **Eclipse Treatment Planning System**	**Comment**
Delineation Method	AI	AI	AI	Not stated	Not stated	The proposed device, primary predicate and one of the reference devices (ART-Plan v1.10.1) share an AI delineation method.
Image registration	Multi-modal and mono-modal. Rigid and deformable Automatic and manual initialization (landmarks, fusion box, alignment). Registration for the purposes of replanning/	**Registration:** CT (including synthetic CT from CBCT), MR and PET	Multi-modal and mono-modal. Rigid and deformable Automatic and manual initialization (landmarks, fusion box, alignment). Registration for the purposes of	NA	CT/MR/PET Image Registration 4D image display (registration of time yes yes series of 3D images)	The proposed device, the primary predicate and most of the reference devices propose registration of medical images of different modalities.

	recontouring and AI-based automatic contouring.		replanning/ recontouring and AI-based automatic contouring.			
Segmentation Features	Automatically delineates OARs and healthy lymph nodes Deep learning algorithm. Automatic segmentation includes the following localizations: * head and neck (on CT images) * thorax/breast (for male/female and on CT images) * abdomen (on CT images and MR images) * pelvis male (on CT images and MR images) * pelvis female (on CT images) * brain (on CT images and MR images)	CT and synthetic CT from CBCT	Automatically delineates OARs and healthy lymph nodes Deep learning algorithm Automatic segmentation includes the following localizations: * head and neck (on CT images) * thorax/breast (for male/female and on CT images) * abdomen (on CT images and MR images) * pelvis male (on CT images and MR images) * pelvis female (on CT images) * brain (on CT images and MR images)	Eclipse also includes tools for treatment preparation (diagnostic image and analysis, contouring and segmentation) and plan review.	Geometrical shapes, Manual editing and manipulation tools, Automatic /semi-automatic tools, Automatic/semi-automatic on-demand and post-processing tools for individual organs/structures, Automatic on-demand and pre-processing tools for multiple organs/structures, 3D Autornargin, Logical operators	The proposed device, the primary predicate and most of the reference devices propose segmentation on medical images of different modalities using AI.
View Manipulation and Volume Rendering	Window and level, pan, zoom, cross-hairs, slice navigation. Color rendering, fused views, gallery views.	Window and level, pan, zoom, cross-hairs, slice navigation. Color rendering, fused views, gallery views.	Window and level, pan, zoom, cross-hairs, slice navigation. Maximum, average and minimum intensity projection (MIP, AVG, MinIP), color rendering, multi-planar reconstruction (MPR), fused views, gallery views.	Not stated	Not stated	The proposed device has the same tools as the primary predicate.

Regions and Volumes of Interest (ROI)	AI Based autocontouring, Registration based contour projection (re-contouring), Manual ROI manipulation and transformation (margins, booleans operators, interpolation).	AI based autocontouring Registration based contour projection (re-contouring) Manual ROI manipulation and transformations (margins, booleans operators, interpolation).	AI Based autocontouring, Registration based contour projection (re-contouring), Manual ROI manipulation and transformation (margins, booleans operators, interpolation).	Not stated	Not stated	Both the proposed device and the primary predicate allow AI automatic contouring and manual contouring.
Region/volume of interest measurements and size measurements	Intensity and Hounsfield units. Size measurements include 2D and 3D measurements (number of slices, volume of a structure, static ruler)	Intensity, Hounsfield units, Size measurement include 2D and 3D measurements (number of slices, volume of a structure, static ruler)	Intensity, Hounsfield units and SUV measurements Size measurements include 2D and 3D measurements (number of slices, volume of a structure, static ruler)	Not stated	Not stated	The proposed device offers the same kind of region/volume of interest measurements and size measurements as the primary predicate.

Device Description:

The ART-Plan application consists of three key modules: SmartFuse,Annotate and AdaptBox, allowing the user to display and visualise 3D multi-modal medical image data. The user may process, render, review, store, display and distribute DICOM 3.0 compliant datasets within the system and/or across computer networks.

Compared to Ethos Treatment Management, 2.1; Ethos Treatment Planning, 1.1 (primary predicate), the following additional feature has been added to ART-Plan v2.1.0:

- generation of synthetic CT from MR images. This does not represent an additional claim as the technological characteristics are the same and it does not raise different questions of safety and effectiveness. Also, this feature is already covered by reference and previous version of the device ART-Plan v1.10.1.

Generation of Synthetic CT	***ART-Plan V2.1.0*** *(Proposed device)*	***Ethos Treatment Management, 2.1; Ethos Treatment Planning, 1.1*** *(primary predicate)*	***ART-Plan v1.10.1*** *(reference device and previous version of the proposed device)*
from MR images	✓		✓
from CBCT images	✓	✓	

The ART-Plan technical functionalities claimed by TheraPanacea are the following:

- Proposing automatic solutions to the user, such as an automatic delineation, automatic multimodal image fusion, etc. towards improving standardization of processes/ performance / reducing user tedious / time consuming involvement.
- Offering to the user a set of tools to assist semi-automatic delineation, semi-automatic registration towards modifying/editing manually automatically generated structures and adding/removing new/undesired structures or imposing user-provided correspondences constraints on the fusion of multimodal images.
- Presenting to the user a set of visualization methods of the delineated structures, and registration fusion maps.
- Saving the delineated structures / fusion results for use in the dosimetry process.
- Enabling rigid and deformable registration of patients images sets to combine information contained in different or same modalities.
- Allowing the users to generate, visualize, evaluate and modify pseudo-CT from MRI and CBCT images.

- Allowing the users to generate, visualize and analyze dose on images of CT modality (only within the AdatpBox workflow)

- Presenting to the user metrics to define if there is a need for replanning or not.

ART-Plan offers deep-learning based automatic segmentation for the following localizations:
- head and neck (on CT images)
- thorax/breast (for male/female and on CT images)
- abdomen (on CT images and MR images)
- pelvis male(on CT images, on synthetic-CT from CBCT and on MR images)
- pelvis female (on CT images)
- brain (on CT images and MR images)

ART-Plan offers deep-learning based synthetic CT-generation from MR images for the following localizations:
- pelvis male
- brain

ART-Plan offers deep-learning based synthetic CT-generation from CBCT images for the following localizations:
- pelvis male

Technological Characteristics:

A comparative review of the ART-Plan with the predicate device found that the technology, mode of operation, and general principles for treatment with this device were substantially equivalent as the predicate device.

Information about our training dataset and generalizability of the models:

A method generalizes well if the observed performance on training and validation sets remains stable. In the case of strong presence of expert's annotation variability (that is not necessarily because of erroneous annotations but because image quality/organ visibility can be interpreted differently among experts), a method that can demonstrate similar performance with respect to a given metric on training, validation and later on testing is considered to generalize well.

In that process, both the loss function being optimized by the optimization procedure (stochastic gradient descent) and the dice metric which is the main proxy of segmentation quality, are monitored over the train and validation sets. If the loss is non-increasing on the validation set and if the dice metrics follow similar in value trends in both the validation and training sets, it is considered that the model being trained does not overfit, and hence should generalize well, at least on input domains similar to ones in those sets.

On the contrary, overfitting can be detected whenever the training loss keeps decreasing while the validation loss after a while increases. This means that the model is focusing on features that are specific to the training data and not present in the validation data. This implies that the capacity of the model to generalize is poor. In that respect, the independence of the train/validation/test sets is fundamental.

We consider that a model is a good candidate for production when the following conditions are met: 1) the loss and dices have reached a plateau on the validation set, 2) there is no overfitting, i.e. training and validation curves are similar and 3) the level of performance of the dice for the different organs are as good or above the clinical expectations according to well defined performance criteria.

The learning curves of organs may be different depending on the sizes and shapes (difficulties) of structures (organs). Thus, the range of testing scores, Dice Similarity Coefficient (DSC), may vary. It is important to remember that smaller organs might have smaller DSC and yet be still clinically relevant and acceptable, as the DSC is a relative metric that is heavily dependent on the volume of the organ. This is due to the fact that the DSC scores are normalized from the union of organ volume between the two sets (ground truth, automatic annotations) and therefore lower DSC could correspond to clinically acceptable values for small organs, since the proposed contours might take just a few editions to make them usable for planning, whilst still saving time from the users, i.e. that these contours would be judged “clinically acceptable after minor corrections” in a qualitative evaluation.

Learning curves can have an average DSC and loss function for each epoch (which is an iteration of training where the whole training dataset has been passed to the network) over the training set and over the validation set. Our curves show that validation and training data are very close to each other, reaching convergence after some epochs (depending on the structure), demonstrating no overfitting of the training data. Once convergence is achieved, the model is considered ready to be tested and clinically validated on a different, yet representative data set, following a well-established process of validation that has already been submitted to and cleared by the FDA.

Some limitations have been identified that correspond either to the sex or the age of patients. For instance, for the auto-segmentation model following limitations are disclosed to the user in the Instruction For Use (User Manual) based on the sex of the patient:

- The Truefisp Pelvis MRI and T2 Elekta Pelvis MRI auto-contouring models only work on male anatomy.
- The patient sex of the patient (dicom tag (0010, 0040)) is taken into account for the auto-segmentation:
    - if the tag is "F" or "M", the sex specific organs (prostate, breast, etc.) are contoured according

to the tag

    - if the tag is empty or "O":
        - if batch: no contour is delineated except external contour
        - if auto segmentation on Annotate: only common contours to the 2 sexes are delineated
    - if the tag is incorrect, the generated contours may be inappropriate

The automatic contouring (including external contour) function may generate inappropriate contours in the following cases:

- When the volume used is an image taken of a child
- When the patient has a particular anatomy.
- When the considered volume is that of a patient not positioned on his back at the time of acquisition.
- When the value entered in the Patient Position tag (0018, 5100) is erroneous.
- When the DICOM-CT contains an unusually high number of slices.
- When the quality of the images used as input is not satisfying enough or the resolution is low such as CBCT. Therefore, the contours produced may have a low quality.
- When the primary volume is an MRI whose acquisition sequence is not compatible with the selected auto-contouring model.

- When the patient is unusually positioned on the image (image not centered on the patient, head rotated on the side...)

Only some anatomies are covered by the automatic contouring:

- Automatic contouring on CT images covers all anatomies (Head & Neck, thorax, breast, abdominal region and pelvis (M/F)
- Automatic contouring on MR images covers some sequences and anatomies: Brain T1, Abdo TF (TrueFisp), Pelvis (male) T2, Pelvis (male) TF.
- Automatic contouring on synthetic-CT from CBCT covers pelvis (male) anatomy.
- In order to suggest the most relevant structures to the user, a CT that does not include a chiasma but does include a liver, is not considered as Head and Neck case. In that case, no Head and Neck structures will be automatically segmented.

All information on the limitations of some models is included in the Instruction For Use (User Manual) which is made available to all users of the software.

- **Summary test statistics or other test results including acceptance criteria or other information supporting the appropriateness of the characterized performance:**

Acceptance criteria for performance of ART-Plan modules were established using performance ranges extracted from benchmark devices and alternative technologies in the literature. For an auto segmentation model to be judged acceptable, every organ included in the model must pass at least one acceptance criterion with success across the different testings it has been submitted to. These criteria are as follows:

a) The Dice Similarity Coefficient (DSC) is equal to or superior to the acceptance criteria set by the AAPM: DSC (mean)≥ 0.8.
Or
b) The Dice Similarity Coefficient (DSC) is equal to or superior to inter-expert variability: DSC (mean)≥ 0.54 or DSC (mean) ≥ mean (DSC inter-expert) + 5% .
Or
c) The clinicians' s qualitative evaluation of the auto-segmentation is considered acceptable for clinical use without modifications (A) or with minor modifications / corrections (B) with a A+B % above or equal to 85% considering the following scale:
A: the contour is acceptable for a clinical use without any modification
B: the contour would be acceptable for clinical use after minor modifications/corrections
C: the contour requires major modifications (e.g. it would be faster for the expert to manually delineate the structure)"

For the SmartFuse module, the acceptance criteria are as follows:

1) ART-Plan SmartFuse produces an anatomical registration of a source image towards a target image for which:
    a) Dice Similarity Coefficient (DSC) of the segmented registered and non registered image is equal to or superior to the acceptance criteria set by the AAPM: DSC(mean)≥0.81
    b) Dice Similarity Coefficient (DSC) of the segmented registered and non registered image is equal to or superior to a benchmark device: DSC(mean)≥0.65
    c) The clinicians' qualitative evaluation of the propagated contours post-registration are considered acceptable for clinical use without

modifications (A) or with minor modifications/corrections (B) with A+B% above or equal to 85% for deformable and above or equal to 50% for rigid registration considering the following scale:
    i) A: the contour is acceptable for a clinical use without any modification
    ii) B: the contour would be acceptable for a clinical use after minor modifications/corrections
    iii) C: the contour requires major modifications (e.g. it would be faster for the expert to manually delineate the structure)

d) The clinicians' qualitative evaluation of the overall registration output following clinical protocols to qualitatively assess registration outcomes is considered acceptable for clinical use with A+B% above or equal to 85% for deformable and 50% for rigid registration considering the following scale:
    i) A: the registration exceeds the expectation
    ii) B: the registration meets the expectation (incl. cases for which additional margin may be required or registration might be relaunched using different supporting tools)
    iii) C: the registration is not acceptable

2) ART-Plan SmartFuse module produces an anatomical registration of a source image towards a target image for which the Jacobian Determinant need to be positive
3) ART-Plan SmartFuse module produces an anatomical registration of a source image towards a target image for which the target registration error (TRE) must be bellow the acceptance criteria set by the AAPM (maximum voxel size of the pair of images involved): TRE<2mm (POPI database)

For the synthetic-CT generation tool from MR, the acceptance criteria are as follows:

a. A median 2%/2mm gamma passing criteria of ≥95%
b. A median 3%/3mm gamma passing criteria of ≥99.0%
c. A mean dose deviation (synthetic-CT compared to standard CT) of ≤2% in ≥88% of patients

For the synthetic-CT generation tool from CBCT, the acceptance criteria are as follows:

a. A median 2%/2mm gamma passing criteria of ≥92%
b. A median 3%/3mm gamma passing criteria of ≥93.57%
c. A mean dose deviation (synthetic-CT compared to standard CT) of ≤2% in ≥76.7% of patients

For the dose engine function, the acceptance criteria are as follows:

a. DVH or median dose deviation ≤24.4% for Lung tissue or ≤4.4% for other organs
b. a median 2%/2mm gamma passing rated of ≥86.3%
c. A median 3%/3mm gamma passing criteria of ≥91.75%

- **Total number of individual patients images in the reported auto segmentation tools and independence of test data and training data**

Our training, validation and test cohorts are built from real-world retrospective data which were initially used for treatment of cancer patients. For the structures of a given anatomy for a given modality (MR or CT), two non-overlapping data sets were separated: the test patients (number selected based on thorough literature review and statistical power) and the train data. We make sure that those sets are non-overlapping and further split the train cases into train and

validation sets and ensure enough train cases for the machine learning models to converge and achieve good performances of the validation set.

We choose the proportion of the training data that is kept as validation set to be between 10% and 25%, depending on the absolute amount of training data. Having more validation data is important to better assess the robustness and generalization of the models as long as enough data is kept for training. This explains that this validation proportion may vary from one task to the other.

- **Auto-segmentation tool**

	Sample Size	%
Training	246226	78
Validation	69147	22
Total	315373	100

- **Synthetic-CT from MR images**

	Sample Size	%
Training	6195	77
Validation	1839	23
Total	8034	100

- **Synthetic-CT from CBCT images**

	Sample Size	%
Training	1467	88
Validation	203	12
Total	1670	100

Table 2: Distribution of samples between training and validation data sets

- **Total number of cases and samples images for training in the reported auto segmentation results**

The total number of patients used for training of auto-segmentation (8950) is lower than the number of samples (246226). This is linked to the fact that one patient can be associated with more images (e.g. CT, MR) and that each image (anatomy) has the delineation of several structures (OARs and lymph nodes) which increases the number of samples used for training and validation. The same rationale for the generation of synthetic-CT from CBCT or MR images.

- **Demographic distribution including gender, age and ethnicity**

All data used for training of the models have been pseudo-anonymised by the centers providing data before transfer. Around 88% of the data used for training contain information on gender and age of the patients. In terms of gender, around 44% and 56% of our data (that contains this information) are from female and male patients, respectively. In comparison, in 2020 according to the Global Cancer Observatory, 48% and 52% of the cancer patients were female and male, respectively.

In terms of age, our data follows the same trend observed and reported in the US (SEER NIH), UK (Cancer Research UK) and worldwide (Global Cancer Observatory) for cancer incidence according to age, with more than 95% of the data coming from patients between 20 and 85 years old. Our data has a slight overrepresentation (8% points) for the ages between 54 and 64 years old, at the cost of a slight underrepresentation of patients in the age range between 20-34 (1.5% points) and above 85 (2.1% points) years old. In addition, following the general global (incl US) trend, our data also depicts a steep rise in the incidence rate from in the age group of 55-64 years old, with a median age of 64 years old (as compared to 66 years old in the US).

Although this information is not exhaustive, this analysis shows that the demographic distribution in terms of age and gender of the data used for training and validation of the models are well aligned with the incidence cancer statistics found for instance in US, UK and globally. This comes from the fact that real clinical data provided by medical facilities without any selection criteria (i.e. no discrimination or selection has been applied to the cases retrieved), leading to the demographic distribution including gender and age across the data is representative of the distribution in the clinic and thus of the cancer patient population in general.

In terms of anatomies, the training data overall is made of 16.4% brain, 28.1% head and neck, 24.6% thorax, 4.4% abdominal and 26.4% pelvis.

An exception is noted for following models that are gender-dependent:
- 100% of pelvis images for male pelvis model for automatic annotation are male patients
- 100% of pelvis images for female pelvis model for automatic annotation are female patients
- 100% of breast images for the breast automatic annotation are female patients
- 100 % of pelvis images for automatic synthetic-CT generation from CBCT and MR are male patients

Since we use pseudo-anonymized data for training and this data does not include any information on ethnicity, TheraPanacea is not able to assess the data distribution and representation in terms of ethnicity.

In addition, automatic delineation of the device demonstrated equivalent performances between non-US and US population.

- **On the “truthing” and data collection process**

    - **Autosegmentation**

The contouring guidelines followed to produce the contours were confirmed with the centers which provided the data. Our truthing process includes a mix of data created by different delineators (clinical experts) and assessment of intervariability, ground truth contours provided by the centers and validated by a second expert of the center, and qualitative evaluation and validation of the contours. This process ensures that the data used for training and testing can be considered representative of the delineation practice across centers and is following international guidelines.

- **Generation of synthetic-CT (from MR or CBCT)**

The clinical evaluation as part of the "truthing-process" guidelines followed to produce and validate the synthetic-CTs were extracted from the literature and confirmed with the centers which provided the data and helped in the performance evaluation. Our truthing process includes imaging metrics based comparison between synthetic-CTs and real planning CTs for the same patients. The real planning CTs come from a mix of machines and centers to avoid any bias. In addition, the evaluation includes a non-inferiority assessment of the capability of the synthetic-CT to be used for dose generation purposes as compared to a planning CT. This process ensures that the data used for training and testing can be considered representative of the clinical practice across centers and following the processes outlined and reviewed through the literature review.

- **On clinical subgroups, confounders and equipment details**

In general, confounding factors affecting health status present in the dataset could be related to patient clinical variables such as age, gender, ethnicity, economical and educational levels. As shown in "Demographic distribution including gender, age and ethnicity", our data is representative of the demographic cancer distribution in terms of gender and age. In addition, our models when appropriate (i.e. for gender independent anatomies) are shared across gender removing any further bias and augmenting substantially training cohorts. To assess potential subgroup bias in AI models, a fairness methodology is used for each subgroup. The analysis raised no significant concerns about the introduction of unfair biases in the AI models for any of the identified subgroups (age and gender).

Variables like ethnicity, economical and educational status that could be associated with obesity are further confounding factors that could impact global patient's anatomy and introduce bias in the performance of the obtained solution. To address this aspect, we have adopted a strategy that projects a patient's specific anatomy to common, multiple, different in size, full-body female and male patient templates, allowing a direct harmonization of data resulting in potential removal of bias of anatomical diversity across ethnic, economical and educational groups. Please note that this information (ethnic group, educational/economical level, etc.) is often not available in the pseudo-anonymised data and therefore performing statistical tests and increasing the number of operations allowing to separate correlations from causality is often unattainable.

Regarding variables associated with treatment therapeutic and treatment implementation strategies; we can imagine imaging devices and treatment devices being potential confounding factors as differences exist among CT and MR scanners manufacturers that could potentially introduce bias. We have addressed this concern through a statistical analysis of the different imaging vendors in EU & USA towards the creation of a data training, validation and testing cohort that globally appropriately represents the market share of the different vendors allowing generalization and removing hardware specific bias. In terms of treatment implementation, it should be noted that different guidelines exist and depending on the treatment device different therapeutic constraints and guidelines are applied. This is reflected in our database since different strategies and constraints are used depending on the choice of treatment (e.g external radiotherapy vs stereotactic treatment). Our solution, due to its concept of removing bias through projection to patient template anatomies as well as due to the component-based approach that is able to aggregate training data across imaging and treatment vendors, is able to address the maximum set of constraints. Therefore, we do not introduce any bias on the type of treatment that will be delivered (supporting any type of clinically conventionally adopted treatment from manufactures such as Varian, Elekta, Accuray, GE, Siemens, ViewRay & Zap

Surgical), providing direct means for customization of the constraints to be met at the clinical expert level and offering a representative coverage of all vendors in radiation oncology world-wide.

An exception is noted for following models that are vendor-, machine- or sequence-dependent:

- MR annotation tool for pelvis and abdominal regions were trained on data from a 0.35T MR machine provided by ViewRay
- synthetic-CT generation tool for pelvis was trained on data from a 0.35T MR machine provided by ViewRay
- synthetic-CT generation tool and annotation tool for MR pelvis was trained on data from 1.5T Philips (Elekta) for T2 sequences, and might not work on T1-weighted images
- synthetic-CT from CBCT generation tool for pelvis male was trained on data coming from Varian and Elekta machines

Summary of Verification and Validation Activities

In Table 3, a summary of Performance Test Results for the Annotate Module of ART-Plan (since the latest cleared version of the software in v1.10.1) is presented:

Organ	Performance test method/Acceptance criterion	Summary of results	Any differences to protocol?
1. Duodenum	Intervariability comparison to experts Criterion C Min sample size for evaluation method: 20	DICE diff inter-expert=1.32% Passed	Sample size: 25 which is above the minimum data sample size
2. Large bowel	Intervariability comparison to experts Criterion C Min sample size for evaluation method: 20	DICE diff inter-expert=1.19% Passed	Sample size: 25 which is above the minimum data sample size
3. Small bowel	Intervariability comparison to experts Criterion C Min sample size for evaluation method: 20	DICE diff inter-expert=2.44% Passed	Sample size: 25 which is above the minimum data sample size
4. Right lacrimal gland	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=100% Passed	Sample size: 20 which is above the minimum data sample size
5. Left lacrimal gland	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=100% Passed	Sample size: 20 which is above the minimum data sample size
6. cervical lymph nodes VIA	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=97% Passed	Sample size: 20 which is above the minimum data sample size
7. Cervical lymph	Qualitative evaluation by experts	A+B=100%	Sample size: 20

nodes VIB	Criterion D Min sample size for evaluation method: 15	Passed	which is above the minimum data sample size
8. Pharyngeal constrictor muscle	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=100% Passed	Sample size: 20 which is above the minimum data sample size
9. Anal canal	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=98.68% Passed	Sample size: 38 which is above the minimum data sample size
10. Bladder	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=93.42% Passed	Sample size: 38 which is above the minimum data sample size
11. Left femoral head	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=100% Passed	Sample size: 38 which is above the minimum data sample size
12. Right femoral head	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=100% Passed	Sample size: 38 which is above the minimum data sample size
13. Penile bulb	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=96.05% Passed	Sample size: 38 which is above the minimum data sample size
14. Prostate	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=92.10% Passed	Sample size: 38 which is above the minimum data sample size
15. Rectum	Qualitative evaluation by experts	A+B=100%	Sample size: 38

	Criterion D Min sample size for evaluation method: 15	passed	which is above the minimum data sample size
16. Seminal vesicle	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=94.59% Passed	Sample size: 37 which is above the minimum data sample size
17. Sigmoid	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=98.68% Passed	Sample size: 38 which is above the minimum data sample size

In Table 4, a summary of Performance Test Results for the SmartFuse module of ART-Plan (since the latest cleared version of the software in v1.10.1) is presented:

Clinical use	Performance test method/Acceptance criterion	Summary of results	Any differences to protocol?
1. tCBCT - sCT	Qualitative evaluation by experts Criterion 1D Min sample size for evaluation method: 15	Rigid: A+B%=95.56% Deformable: A+B%=97.78% Passed	Sample size: 45 which is above the minimum data sample size
2. tsynthetic-CT - sCT	Qualitative evaluation of propagated contours by experts Criterion 1C Min sample size for evaluation method: 17	Deformable: Target: A+B%=94.06% Passed	Sample size: 30 which is above the minimum data sample size
3. tCT - sSCT	Qualitative evaluation by experts Criterion 1D Min sample size for evaluation method: 17	rigid: A+B%=70.37% Passed	Sample size: 27 which is above the minimum data sample size

In Table 5, a summary of Performance Test Results for the AdaptBox module of ART-Plan (since the latest cleared version of the software in v1.10.1) is presented:

Criteria	Performance test method/Acceptance criterion	Summary of results	Any differences to protocol?
Synthetic-CT from CBCT			
Gamma index 2%/2mm 3%/3mm	Criteria A & B Min sample size for evaluation method: 17	2%/2mm = 98.85 3%/3mm = 99.43 Passed	Sample size: 20 which is above the minimum data sample size
DVH parameters (PTV)	Criterion C Min sample size for evaluation method: 17	DVH parameters < 0.199% in 100% of the cases Passed	Sample size: 20 which is above the minimum data sample size
Dose engine			
Gamma index 2%/2mm 3%/3mm	Criteria B & C Min sample size for evaluation method: NA in the state of the art	2%/2mm = 97.22% 3%/3mm = 99.50% Passed	Sample size: 272 total Brain: 42 H&N: 70 Chest: 44 Breast: 26 Pelvis 90
DVH parameters (PTV)	Criteria A Min sample size for evaluation method: NA in the state of the art	DVH parameters < 1.29% Passed	Sample size: 272 total Brain: 42 H&N: 70 Chest: 44 Breast: 26 Pelvis 90
DVH parameters (OARs)	Criteria A Min sample size for evaluation method: NA in the state of the art	DVH parameters < 3.9% Passed	Sample size: 272 total Brain: 42 H&N: 70 Chest: 44 Breast: 26 Pelvis 90

Non-Clinical Tests (Performance/Physical Data):

In Table 6, testing based on which ART-Plan v2.1.0 (since the latest cleared version of the software in v1.10.1) was evaluated for its safety and effectiveness are presented:

Test Name	Test Description/Results	Results
Usability Report (V2.1.0)	This document is intended to document the usability test results for the ART-Plan v2.1.0 for compliance with IEC 62366-1:2015+AMD1:2020 - Medical devices - Application of usability engineering to medical devices.	Passed
Usability file - ART-USR-13 (V2.1.0)	The ART-Plan was assessed with regards to usability for compliance with each section of IEC 62366.	Passed
Usability - Testers qualification (V2.1.0)	This table shows that European medical physicists who have participated in the evaluation have at least an equivalent expertise level compared to a junior US medical physicist (MP), and responsibilities in the radiotherapy clinical workflow are equivalent.	N/A
Literature Review and Performance Criteria Extraction Report for ART-Plan (V2.1.0)	A literature review is performed to establish acceptance criteria for performance of ART-Plan modules using performance ranges observed from benchmark devices and alternative technologies in the literature. All measures of performance that were established in this document were supported by clinical evidence. It was also demonstrated, from the clinical data, that ART-Plan has a clear clinical relevance in accordance with the clinical state of the art.	N/A
ART-Plan performance testing - Overview (V1.10.1-2.1.0)	The document summarises all performance tests that have been performed since the last FDA approved version (1.6.1). It also shows which criteria have been met in each test for all modules of ART-Plan. It demonstrates that all modules of ART-Plan pass at least one performance acceptance criterion and hence are clinically acceptable for release.	Passed
Pilot study for sample size estimation - literature review (V2.1.0)	The literature review was performed to estimate the appropriate sample size of the testing data set towards demonstrating the performance of the image registration, segmentation and synthetic-CT generation solutions on the basis of the most recent and most relevant scientific literature.	N/A
Qualitative & Quantitative validation of fusion performances (V2.1.0)	The study was developed to cover the major clinical use cases in which fusions are used in the radiotherapy workflow and split into as many sub-studies as clinical use cases of fusion in radiotherapy workflow. The results show that both types of fusion algorithms (Rigid & Deformable) in SmartFuse pass the performed tests, and provide valid results for further clinical use in radiotherapy.	Passed
Protocol for qualitative & quantitative validation of fusion performances for tCBCT_sCT_replanning modality (V2.0.0)	This study evaluated the quality of the rigid and the deformable fusion algorithms of the SmartFuse module for replanification of CT-based treatments.	Passed

Protocol for qualitative & quantitative validation of fusion performances for tsynthetic-CT_sCT_replanning modality (V2.1.0)	This study evaluated the quality of the rigid and the deformable fusion algorithms of the SmartFuse module for replanification of CT-based treatments.	Passed
Protocol for qualitative & quantitative validation of fusion performances for tCT_ssynthetic-CT_replanning modality (V2.1.0)	This study evaluated the quality of the rigid and the deformable fusion algorithms of the SmartFuse module for replanification of CT-based treatments.	Passed
Study Protocol and Report Annotate Performances Summary (V2.1.0)	The purpose of this document is to describe all the testing protocols and testing results for validating the performance of the Annotate module. To this aim, this document gathers information of all the different testing conducted on Annotate for the CT, MR and synthetic-CT from CBCT autosegmentation algorithms for v2.1.0: ● qualitative evaluation for autosegmentation performance - pelvis male organs on synthetic-CT from CBCT - see section 18.13 ● autosegmentation performances against inter-expert variability - bowel loop structures on CT - see section 18.14 ● qualitative evaluation for autosegmentation performance - H&N lymph nodes (CT) - see section 18.15 ● Non regression testing for integration in ART-Plan v1.11.0 (CT and MR models) - see section 18.7 ● Non regression testing for integration in ART-Plan v2.1.0 (CT and MR models) - see section 18.16 Since all organs added in v.2.1.0 of Annotate have passed at least one test and met at least one acceptance criteria, all organs have been released.	Passed
Study Protocol and Report Qualitative Validation of Annotate in ART-Plan for pelvis male organs on synthetic-CT from CBCT (V2.1.0)	This test demonstrates that the module Annotate provides acceptable contours for the organs evaluated on synthetic-CT from CBCT images of patients. All organs that have passed the acceptance criterion of reaching a percentage of at least 85% of A or B (qualitative evaluation) have been released in v.2.1.0.	Passed
Study Protocol and Report-Autosegmentation performances against inter-expert variability - bowel loop structures (V2.1.0)	This test demonstrates that the module Annotate provides clinically acceptable (compared to inter-expert variability) for bowel loops structure. All organs that have passed the acceptance criterion of reaching a percentage of a DSC(mean)≥ 0.8 or DSC(mean)≥0.54) or DSC(mean)≥mean(DSC inter-expert)+5% relative error (quantitative evaluation) have been released in v.2.1.0.	Passed
Study Protocol and Report Qualitative Validation of Annotate in ART-Plan for H&N lymph nodes (V2.1.0)	This test demonstrates that the module Annotate provides acceptable contours for the organs evaluated on CT images of patients. All organs that have passed the acceptance criterion of reaching a percentage of at least 85% of A or B (qualitative evaluation) have been released in v.2.1.0.	Passed

Autosegmentation regression test for integration in ART-Plan (V2.1.0)	This test demonstrates equivalence between the version v.2.1.0 and v.2.0.0 of the auto-segmentation models for all structures and shows that the updated models provide clinically acceptable contours. All organs passed the defined criteria, and were hence accepted for release in the v.2.1.0.	Passed
Study protocol and report Dose engine measurements validation (V2.1.0)	The evaluation demonstrated the dose calculation accuracy by carrying out measurements on a Linac and comparing the results with the dose engine given various metrics and acceptance criteria.	Passed
Study protocol and report Dose engine clinical validation (V2.1.0)	The evaluation demonstrated the non-inferiority of the dose engine function of the AdaptBox module in terms of dosimetric measures compared to other commercially available dose engines.	Passed
Study protocol and report Dose engine performance against reference devices (V2.1.0)	The evaluation demonstrated the non-inferiority of the dose engine function of the AdaptBox module in terms of dosimetric measures compared to FDA cleared devices.	Passed
Study protocol and report Clinical validation of synthetic-CTs from CBCT (V2.1.0)	The evaluation demonstrated the non-inferiority of using synthetic-CT from CBCT for treatment replanning in terms of dosimetric measures as compared to CT-based treatment replanning. Our synthetic-CT from CBCT for pelvis has shown to produce results that meet the acceptance criteria derived from clinical practice and literature review.	Passed
Study protocol and report Performance against Ethos (Varian) (V2.1.0)	The evaluation demonstrated the non-inferiority of the AdaptBox module compared to a FDA cleared device.	Passed
Study protocol and report Performance on US data (V2.1.0)	The evaluation demonstrated the equivalent performances between non-US and US population.	Passed
Study Protocol and Report for CBCT-based synthetic-CT evaluation (V2.1.0)	The evaluation demonstrated the anatomical and geometrical of the synthetic-Ct generated from CBCT	Passed
AI-powered decision making process for RT re-planning (V2.1.0)	This study demonstrated that AdaptBox is an effective tool to assist physicians and physicists in the decision making process for re-planning	Passed
System Verification and Validation Testing (V2.1.0)	The system verification and validation testing was performed to verify the software of the ART-Plan.	Passed

Software Verification and Validation Testing

Software verification and validation testing were conducted, and documentation was provided as recommended by FDA's Guidance for Industry and FDA Staff, "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices."

The software for this device was considered as a "major" level of concern, since a failure or latent design flaw could directly result in death or serious injury to the patient or a failure or provide diagnostic information that directly drives a decision regarding treatment or therapy, such that if misapplied it could result in serious injury or death.

Animal Studies

No animal studies were conducted as part of submission to prove substantial equivalence.

Clinical Studies

No clinical studies were conducted as part of submission to prove substantial equivalence.

Safety and Effectiveness/Conclusion:

Based on the information presented in these 510(k) premarket notifications the TheraPanacea ART-Plan is considered substantially equivalent. The TheraPanacea ART-Plan is as safe and effective as the currently marketed predicate device.

Based on testing and comparison with the predicate devices, TheraPanacea ART-Plan indicated no adverse indications or results. It is our determination that the TheraPanacea ART-Plan performs within its design specifications and is substantially equivalent to the predicate device.