Therapanacea SAS
% Catherine Martineau-Huynh
COO
7 bis boulevard Bourdon
Paris, 75004
FRANCE

April 19, 2023

Re: K230023/S001
Trade/Device Name: ART-Plan
Regulation Number: 21 CFR 892.2050
Regulation Name: Medical Image Management And Processing System
Regulatory Class: Class II
Product Code: QKB, MUJ, LLZ
Dated: December 28, 2022
Received: January 4, 2023

Dear Catherine Martineau-Huynh:

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 (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 located 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.

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 and Part 809); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for devices or postmarketing safety reporting (21 CFR 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 4, Subpart A) for combination products; and, if applicable, the electronic product radiation control provisions (Sections 531-542 of the Act); 21 CFR 1000-1050.

Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21 CFR Part 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 -S

Digitally signed by Lora D. Weidner -S
Date: 2023.04.19 18:00:58 -04'00'

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)*
K230023

Device Name
ART-Plan

Indications for Use *(Describe)*
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, 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 mport, define, display, transform and store DICOM3.0 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.

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.

TheraPanacea SAS
Special 510(k)
For ART-Plan v1.10.1

K230023

510(k) Summary

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

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirement of 21 CFR 807.92

Submitter Information:	
Name:	TheraPanacea SAS
Address:	7 bis boulevard Bourdon 75004 Paris
Establishment Registration Number:	3019834893
Owner/Operator Number:	10082087
Phone:	+33 9 62 52 78 19
Contact:	Catherine Martineau-Huynh
E-mail:	c.huynh@therapanacea.eu
Date of Summary:	28th of December 2022

Device Information:

Below summarises the Device Classification information regarding the ART-Plan v1.10.1.

Device Proprietary Name	NA
Common Name:	ART-Plan
Trade Name:	ART-Plan
Product Code(s):	NA

Primary Product Code

Regulation Number	Device	Device Class	Product Code	Classification Panel
892.2050	Medical image management and processing system	Class II	QKB	Radiology

Secondary Product Codes

Regulation Number	Device	Device Class	Product Code	Classification Panel
892.2050	Medical image management and processing system	Class II	LLZ	Radiology
892.5050	Medical charged-particle radiation therapy system	Class II	MUJ	Radiology

TheraPanacea SAS
Special 510(k)
For ART-Plan v1.10.1

Substantial Equivalence

Manufacturer	Trade Name	Product Code	Regulation	510(k) Number
TheraPanacea SAS	ART-Plan	QKB	892.2050	K220813

Submission Description

This Special 510(k) covers a modification to add 48 new structures to existing localizations and 8 bug fixes to ART-Plan v1.10.0, as cleared in 510(k) (K220813).

There are no significant changes presented to the other software components previously cleared in K220813 i.e., no change to the other modules such as Smartfuse, Home, Administration and to the other features such as generation of synthetic CT from MR.

Well-established methods described in the previously 510(k)-cleared ART–Plan v1.10.0, have been used to evaluate the change is provided in a summary in this submission.

This Special 510(k) presents the addition of 48 new structures to existing localizations (Annotate module). This modification extends the use of Annotate to other radiotherapy protocols, such as the SBRT for lung. It also includes 8 bug fixes.

Device Description

- **General Description**

The ART-Plan application consists of two key modules: SmartFuse and Annotate, allowing the user to display and visualize 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. Supported modalities cover static and gated CT (computerized tomography including CBCT and 4D-CT), PET (positron emission tomography) and MR (magnetic resonance).

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 images.

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 and 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

Intended/ Indications for Use

Intended use :

ART-Plan is a software for multi-modal visualization, contouring and processing of 3D images of cancer patients for whom 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 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, 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 DICOM3.0 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.

Comparison with the Predicate and Previously Cleared Device

The candidate device TheraPanacea SAS ART-Plan 1.10.1 is substantially equivalent to the predicate, K220813, the TheraPanacea SAS ART-Plan 1.10.0 and a comparison of the key characteristics is summarised in Table 1.

Characteristic	ART-Plan v1.10.1 with Modification	ART-Plan v1.10.0 K220813 (Predicate)	Equivalence
Device Name	ART-Plan v1.10.1	ART-Plan v1.10.0	Equivalent
Manufacturer	TheraPanacea SAS	TheraPanacea SAS	Equivalent
Device Classification	II	II	Equivalent
Primary Product Code	QKB	QKB	Equivalent
Secondary Product Code	LLZ, MUJ	LLZ, MUJ	Equivalent
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, 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	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, 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	Equivalent

Characteristic	ART-Plan v1.10.1 with Modification	ART-Plan v1.10.0 K220813 (Predicate)	Equivalence
	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	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	
Intended user/Location	It is intended to be used by trained medical professionals including, but not limited to, radiologists, radiation oncologists, dosimetrists, and medical physicists / Hospitals	It is intended to be used by trained medical professionals including, but not limited to, radiologists, radiation oncologists, dosimetrists, and medical physicists / Hospitals	Equivalent
Segmentation features (Annotate module)	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)	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)	Equivalent - The candidate device and predicate are capable of automatically contouring the organ-at-risk (OAR) and healthy lymph nodes using AI (deep learning) algorithm. The candidate device includes 48 additional structures to the already existing localizations
Bugs	Correction of 8 bugs	NA	Equivalent The bug fixes introduced in the candidate device do not affect the safety or performance of the predicate device

Table 1: Comparison of characteristics between the Modified System and the Predicate System.

In Table 2, structures included in ART-Plan v1.10.1 are presented.

Head & Neck (CT) - 47 structures						
Brainstem	Cerebellum	Chiasma	Encephalon	Esophagus	Hypophyse	Larynx
Left Brachial plexus	Left cervical lymph node IB	Left cervical lymph node II	Left cervical lymph node III	Left cervical lymph node IVA	Left cervical lymph node IVB	Left cervical lymph node V
Left cervical lymph node VIIA	Left cervical lymph node VIIB	Left cochlea	Left eye	Left eye lens	Left optical nerve	Left parotid
Left submandible	Left temporomandibular joints	Lips	Mandible	Medullar canal	Mouth	Right brachial plexus
Right cervical lymph node IB	Right cervical lymph node II	Right cervical lymph node III	Right cervical lymph node IVA	Right cervical lymph node IVB	Right cervical lymph node V	Right cervical lymph node VIIA
Right cervical lymph node VIIB	Right cochlea	Right eye	Right eye lens	Right optical nerve	Right parotid	Right submandible
Right temporomandibular joints	Spinal Cord	Thyroid	Trachea	External contour		
Thorax / Breast (CT) - 30 structures						
Esophagus	Heart	Larynx	Left brachial plexus	Left breast	Left humeral head	Left IMC (internal mammary chain) lymph node
Left interpectoral lymph node	Left lung	Left lymph node L1	Left lymph node L2	Left lymph node L3	Left supraclavicular lymph nodes	Liver
Medullar canal	Right brachial plexus	Right breast	Right humeral head	Right IMC (internal mammary chain) lymph node	Right interpectoral lymph node	Right lung
Right lymph node L1	Right lymph node L2	Right lymph node L3	Right supraclavicular lymph nodes	Spinal cord	Thoracic aorta	Thyroid
Trachea	External Contour					
Pelvis Male (CT) - 19 structures						
Anal canal	Bladder	Bowel bag	CTVn prostate	Left femoral head	Left iliac	Left kidney
Liver	Medullar canal	Penile bulb	Prostate	Rectum	Right femoral head	Right iliac
Right kidney	Seminal vesicle	Sigmoid	Spinal cord	External contour		
Pelvis Female (CT) - 25 structures						
Anal canal	Bladder	Bowel bag	Common iliac gyneco lymph node	CTVt gyneco	Left femoral head	Left iliac
Left iliac gyneco lymph node	Left inguinal gyneco lymph node	Left kidney	Liver	Lomboaortic lymph node	Medullar canal	Parametrium

Presacral gyneco lymph node	Rectum	Right femoral head	Right iliac	Right iliac gyneco lymph node	Right inguinal gyneco lymph node	Right kidney
Sigmoid	Spinal cord	Vagina	External contour			
Heart substructures (part of thorax / breast) (CT) - 13 structures						
Ascending aorta	Coronary sinus	Left atrium	Left main coronary artery	Left ventricle	Left ventricle anterior	Left ventricle apical
Left ventricle inferior	Left ventricle lateral	Left ventricle septal	Right atrium	Right ventricle	Vena cava superior	
SBRT lung (part of thorax / breast) (CT) - 14 structures						
Bronchial tree	Carina	Left anterior descending aorta	Left bronchia	Left bronchus	Left chest wall	Pericardium
Pulmonary arteries	Right bronchia	Right bronchus	Right chest wall	Spleen	Stomach	Vena cava inferior
Brain T1 (MR) - 28 structures						
Anterior cerebellum	Chiasma	Encephalon	Hypophyse	Left cochlea	Left cornea	Left eye lens
Left hippocampus	Left hypothalamus	Left lacrimal gland	Left optical nerve	Left retina	Left vestibular semicircular canals (VSCC)	Medulla oblongata
Midbrain	Pons	Posterior cerebellum	Right cochlea	Right cornea	Right eye lens	Right hippocampus
Right hypothalamus	Right lacrimal gland	Right optical nerve	Right retina	Right versibular semicircular canals (VSCC)	Spinal cord	External contour
Pelvis T2 (male) (MR) - 12 structures						
Anal canal	Bladder	Left femoral head	Left pelvis	Penile bulb	Prostate	Rectum
Right femoral head	Right pelvis	Sacrum	Seminal vesicle	External contour		
Pelvis TF (male) (MR) - 19 structures						
Anal canal	Aorta	Bladder	Duodenum	Inferior vena cava	Large bowel	Left femoral head
Left kidney	Liver	Pancreas	Penile bulb	Prostate	Rectum	Right femoral head
Right kidney	Seminal vesicle	Sigmoid	Stomach	External contour		

Table 2: Structures included in ART-Plan v1.10.1

Technological Characteristics

The proposed modification to the Annotate module on the TheraPanacea ART-Plan v1.10.1 has identical indications for use, operating principles, performance, and technical specification as the predicate device, the TheraPanacea SAS ART-Plan 1.10.0.

The proposed modification of the addition of 48 new structures to the existing localizations and the introduction of 8 bug fixes enables further help in the management of radiotherapy planning. Equivalence between both systems has been shown through the thorough performance testing performed.

Summary of Non-Clinical Tests (Performance data)

The TheraPanacea ART-Plan V1.10.1 was tested to ensure performance of the system, to verify and validate the product design and to characterise the performance and safety of TheraPanacea's ART-Plan v1.10.1.

The performance of the Annotate module modification is identical to the predicate previously cleared device in terms of technical specification and safety. The primary difference between the predicate and the candidate devices is the addition of 48 new structures to existing localizations (Annotate module). This modification extends the use of Annotate to other radiotherapy protocols, such as the SBRT for lung,

All changes were verified and validated according to TheraPanacea SAS internal design control process and in accordance with special controls for software systems.

This is demonstrated through the extensive testing carried out on the system with the modification, which passes all performance and verification tests that follow the same protocol and acceptance criteria as the ones submitted to the FDA under the clearance of the predicate device (K220813). It also demonstrated that the proposed modification performed according to its specification and has met the technological and performance criteria which have not changed from the predicate device.

Information about our training dataset:

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, as described in the process 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, 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 T2, Pelvis TF.
- 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 the above 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 synthetic-CT generation tool, 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 (pseudo-CT compared to standard CT) of ≤2% in ≥88% of patients

- **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.

	Sample size	%
Training	299 142	0.8
Validation	75 018	0.2
Total	274 160	1

Table 3: Distribution of samples between training and validation data sets

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

The total number of patients used for training (8736) is lower than the number of samples (374160). 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.

- **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 80% 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 60 years old, at the cost of a slight underrepresentation of patients in the age range between

20-34 (1.5% points) and above 85 (6.5% 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 63 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.

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 are male patients

The pseudo-anonymized data did not include any information on the ethnicity.

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

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

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.

- **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.

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), 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

- **On generalizability of the models:**

A method generalizes well also 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.

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.

Once convergence is achieved, the model is 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.

Summary of Verification and Validation Activities

Organ	Performance test method/Acceptance criterion	Summary of results	Any differences to protocol?
1. Carina	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=6.58% Passed	Sample size: 33 which is above the minimum data sample size
2. Lad coronary	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=15.56% Passed	Sample size: 33 which is above the minimum data sample size
3. Left bronchia	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=14.75% Passed	Sample size: 33 which is above the minimum data sample size
4. Left bronchus	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=6.17% Passed	Sample size: 33 which is above the minimum data sample size
5. Left chest wall	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=0% Passed	Sample size: 33 which is above the minimum data sample size
6. Pericardium	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=1.06% Passed	Sample size: 33 which is above the minimum data sample size
7. pulmonary	Intervariability comparison to	DICE diff	Sample size: 33

arteries	experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	inter-expert=3.61% Passed	which is above the minimum data sample size
8. Right bronchia	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=22.64% Passed	Sample size: 33 which is above the minimum data sample size
9. Right bronchus	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=7.41% Passed	Sample size: 33 which is above the minimum data sample size
10. Right chestwall	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=-1.10% Passed	Sample size: 33 which is above the minimum data sample size
11. Spleen	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=1.08% Passed	Sample size: 33 which is above the minimum data sample size
12. stomach	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=2.27% Passed	Sample size: 33 which is above the minimum data sample size
13. Vena cava inf	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=9.59% Passed	Sample size: 33 which is above the minimum data sample size

14. Bronchial tree	This structure corresponds to a boolean of other structures: carina + leftbronchus + rightbronchus + leftbronchia + rightbronchia which which have all passed the performance tests		
15. Ascending aorta	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
16. coronary sinus	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	diff inter-expert=3.59% Passed	Sample size: 20 which is the minimum data sample size
17. Left atrium	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
18. Left main coronary artery	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=93% Passed	Sample size: 20 which is above the minimum data sample size
19. Left ventricle	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
20. Left ventricle anterior	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
21. Left ventricle apical	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

22. Left ventricle inferior	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
23. Left ventricle lateral	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
24. Left ventricle septal	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
25. Right atrium	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
26. Right ventricle	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
27. Vena cava sup	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
28. Left cervical lymph node IVB	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B = 96.67% Passed	Sample size: 15 which is above the minimum data sample size
29. Right cervical lymph node IVB	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B = 96.67% Passed	Sample size: 15 which is above the minimum data sample size

30. Anterior cerebellum	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=6.47% Passed	Sample size: 30 which is above the minimum data sample size
31. Left cochlea	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=19.96% Passed	Sample size: 30 which is above the minimum data sample size
32. Left cornea	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=7.93% Passed	Sample size: 30 which is above the minimum data sample size
33. Left hypothalamus	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=4.19% Passed	Sample size: 30 which is above the minimum data sample size
34. Left lacrimal gland	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=4.76% Passed	Sample size: 30 which is above the minimum data sample size
35. Left retina	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=12.26% Passed	Sample size: 30 which is above the minimum data sample size
36. Left vscc	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=-1.20% Passed	Sample size: 30 which is above the minimum data sample size

37. Medulla oblangata	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=3.25% Passed	Sample size: 30 which is above the minimum data sample size
38. Midbrain	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=5.78 Passed	Sample size: 30 which is above the minimum data sample size
39. Pons	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=3.39% Passed	Sample size: 30 which is above the minimum data sample size
40. Posterior cerebellum	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=2.07% Passed	Sample size: 30 which is above the minimum data sample size
41. Right cochlea	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=29.22% Passed	Sample size: 30 which is above the minimum data sample size
42. Right cornea	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=4.66% Passed	Sample size: 30 which is above the minimum data sample size
43. Right hypothalamus	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=3.32% Passed	Sample size: 30 which is above the minimum data sample size

44. Right lacrimal gland	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=4.23% Passed	Sample size: 30 which is above the minimum data sample size
45. Right retina	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=10.03% Passed	Sample size: 30 which is above the minimum data sample size
46. Right vscc	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=3.08% Passed	Sample size: 30 which is above the minimum data sample size
47. Spinal Cord	Intervariability comparison to experts (Criterion C of performance criteria) Min sample size for evaluation method: 20	DICE diff inter-expert=13.01% Passed	Sample size: 30 which is above the minimum data sample size
48. Sigmoid	Qualitative evaluation by experts Criterion D Min sample size for evaluation method: 15	A+B=100% Passed	Sample size: 30 which is above the minimum data sample size

Table 4: Summary of Performance Test Results for the Annotate Module of ART-Plan

Summary of Non-Clinical Tests (Performance data)

The TheraPanacea ART-Plan V1.10.1 was tested to ensure performance of the system, to verify and validate the product design and to characterise the performance and safety of the TheraPanacea ART-Plan v1.10.1.

The performance of the Annotate module modification is identical to the predicate previously cleared device in terms of technical specification and safety. The primary difference between the predicate and the candidate devices is the addition of 48 new structures to existing localizations (Annotate module). This modification extends the use of Annotate to other radiotherapy protocols, such as the SBRT for lung.
All changes were verified and validated according to TheraPanacea SAS internal design control process and in accordance with special controls for software systems.

This is demonstrated through the extensive testing carried out on the system with the modification, which passes all performance and verification tests that follow the same protocol and acceptance criteria as the ones submitted to the FDA under the clearance of the predicate device (K220813). It also demonstrated that the proposed modification performed according to its specification and has met the technological and performance criteria which has not changed from the predicate device.

As part of a “standard” lifecycle of a software, bugs were fixed (8 bug fixes). System verification and validation testing were performed to verify the software of the TheraPanacea ART-Plan v1.10.1 after the bug fixes using the same verification tests and acceptance criteria as the ones submitted to the FDA under the clearance of the predicate device (K220813). Related documents are available on request.

Table 5 summarises the non-clinical tests (performance tests) completed by TheraPanacea to validate the organs added in v1.10.1.

Test Name	Test Description	Results
Study Protocol and Report Annotate Performances Summary (v1.10.1)	The purpose of this document is to describe the testing protocols and testing results for validating the performance of the Annotate module. The performance study of the ART-Plan module, Annotate, evaluates the precision of the contours done by the software either i) against the one done by human experts through a direct comparison or ii) by a qualitative validation done by human experts. The objective of the tests is to demonstrate that the auto-segmentation algorithms (CT and MR) of the module Annotate pass at least one acceptance criterion. This document includes test procedures, documentation, references, specifications, and acceptance criteria. This document is updated to take into account modifications made in ART-Plan v1.10.1 with the addition of heart substructures and SBRT in the CT automatic segmentation.	Passed
Study Protocol and Report quantitative validation of Annotate	This test demonstrates that the Annotate provides clinically acceptable (compared to inter-expert variability) for SBRT structures. All organs that have passed the acceptance	Passed

Test Name	Test Description	Results
in ART-Plan v1.10.1 for SBRT CT.	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.1.10.1.	
Study Protocol and Report Qualitative Validation of Annotate in ART-Plan V1.10.1 for Heart substructures CT	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.1.10.1.	Passed

Table 5: Summary of non-clinical performance tests performed for ART-Plan v1.10.1

Summary of Animal & Clinical Studies

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

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

Safety and Effectiveness/ Conclusion

Based on the information presented in this Special 510(k) submission, the TheraPanacea SAS ART-Plan v.1.10.1 is considered substantially equivalent. The TheraPanacea ART-Plan is as safe and effective as the currently marketed predicate device, TheraPanacea SAS ART-Plan v1.10.0 previously 510(k) cleared (K220813) .

Based on testing and comparison with the predicate device TheraPanacea SAS ART-Plan v1.10.0 previously 510(k) cleared (K220813), TheraPanacea SAS ART-Plan v1.10.1 indicated no adverse indications or results. It is our determination that the TheraPanacea SAS ART-Plan v.1.10.1 performs within its design specifications and is substantially equivalent to the predicate device, TheraPanacea SAS ART-Plan v1.10.0 previously 510(k) cleared (K220813).