510(k) EXECUTIVE SUMMARY

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

Submitter: One Lambda, Inc.
22801 Roscoe Blvd
West Hills, CA 91304

Contact Information:

Primary Contact

Name: Sheryl Skinner
Title: Director, Regulatory and Clinical Affairs
Address: One Lambda, Inc.
22801 Roscoe Boulevard
West Hills, CA 91304
USA
Tel: 1 (202) 415-5866
Email: sheryl.skinner@thermofisher.com

Alternative Contact

Name: Angela Estany
Title: Sr. Director, Quality and Regulatory Affairs
Address: One Lambda, Inc.
22801 Roscoe Boulevard
West Hills, CA 91304
USA
Tel: 1 (747) 494-1346
Email: angela.estany@thermofisher.com

Date prepared: 17 May 2024

Device Trade Name: SeCore™ CDx HLA Sequencing System

Common Name(s): HLA Sequencing
SeCore CDx
GSSP (Group Specific Sequencing Primers)
Sanger Sequencing
Sequence Based Typing (SBT)
uTYPE CDx

Classification Name: Human Leukocyte Antigen Typing Companion Diagnostic Test

Classification/Product Code: Class II, QUK

Predicate Device: SeCore™ CDx HLA Sequencing System, De Novo, BR220737

1. Device Information

1.1 Device Description

The SeCore CDx HLA Sequencing System uses a sequence-based typing (SBT) method to detect HLA-A alleles in genomic DNA purified from whole blood specimens. This technology uses polymerase chain reaction (PCR), where denatured single stranded DNA is hybridized to oligonucleotide primers. In an automated procedure, new strands of DNA are synthesized by a heat-resistant enzyme (Taq polymerase) through utilization of a pool of deoxyribonucleotide triphosphates (dNTPs).

During PCR amplification with the Veriti™ Dx Thermocycler, specifically designed SeCore CDx HLA Sequencing Kit primers ensure only specific HLA alleles or groups of alleles are amplified. The effectiveness of the PCR process is checked by passing a portion of the reaction through an agarose gel to separate the reaction products. The success of the PCR reaction is gauged by the presence or absence of appropriate band sizes when visualized under ultraviolet (UV) light.

For DNA sequencing, the remaining reaction product is treated with exonuclease I and shrimp alkaline phosphatase (SAP), which degrades unincorporated primers and dephosphorylates unused dNTPs. BigDye™ Terminator Sanger sequencing chemistry is then used to generate fluorescent-labeled DNA fragments, which are separated by capillary electrophoresis using the 3500 Dx / 3500xl Dx Genetic Analyzer CS2.

Output files from the sequencing instrument (.ab1) are analyzed using the uTYPE CDx HLA Sequence Analysis Software. This software is provided to the user to evaluate HLA typing results by matching the sequencing results to known HLA type allele sequences listed in the IMGT (International lmMunoGeneTics) histocompatibility database. The output of the uTYPE CDx HLA Sequence Analysis Software is a report that indicates detected HLA alleles.

The SeCore™ CDx HLA Sequencing System consists of the following items.

Table 1: SeCore CDx HLA Sequencing System Device Information

Catalog ID (SKU)	Kit Name	Analyte	Configuration
SECCDX-A	SeCore™ CDx HLA A Locus Sequencing Kit	HLA-A	25 Test
SECCDX-GSSP	SeCore™ CDx HLA GSSP Kit	HLA-A	25 Test
UTPCDX-PGR	uTYPE™ CDx HLA Sequence Analysis Software	N/A	N/A

Each SeCore CDx HLA-A Locus Sequencing kit includes the following:

- HLA-A Locus Specific Amplification Mixture
- FastStart™ Taq DNA polymerase enzyme for PCR amplification
- ExoSAP-IT™ reagent
- HLA -A Locus Specific Sequencing Mixtures (containing locus specific sequencing primers, dye terminators, and sequencing enzyme)
- Precipitation (PPT) buffer

Each SeCore CDx HLA GSSP Kit includes the following:

- Group Specific Sequencing Primer (GSSP) Mixtures
- BigDye™ Terminator
- Precipitation (PPT) buffer

Figure 1: Representative Image of a SeCore CDx HLA Sequencing Kit – Box with Reagent Vials

1.2 Operational Parameters

Table 2: Instrumentation Associated with the SeCore CDx HLA Sequencing System

Catalog/Model Number	Device Description	Marketing Status
A46344 (8-capillary) A46345 (24-capillary)	Applied Biosystems 3500 Dx Genetic Analyzer Applied Biosystems 3500 xL Dx Genetic Analyzer	Product code: PCA Class 2 Device 510(k)-cleared (Refer to BK110039)
4452300 / Model 9912	Veriti Dx 96-Well Thermal Cycler	Class I Device

Specimen Collection

- Blood samples should be collected in ACD or EDTA anticoagulated tubes
- Do not use heparinized samples
- Phenol, ethanol, and SDS may cause inhibition of PCR (refer to Product Insert)

DNA Sample Purity and Stock Solution

- OD260/280 ratio above 1.7-1.9
- Optimal DNA concentration of 20ng/µL
- Resuspend in water for immediate use or TE-4 buffer

Manufacturing workflows for the SeCore CDx HLA Sequencing Kit and accessory SeCore CDx HLA GSSP Kit are described in the Principles of Operations section in attachment *009_SeCore CDx Device Description and Principles of Operations*, Figure 1 to Figure 6. Submitted process flowcharts describe the manufacturing, quality control testing, and release of the product. All raw material buffers, primers, enzymes, and other components are purchased, and qualified upon incoming receipt.

As part of the manufacturing process, individual lots of oligonucleotide primers are qualified and then all components are dispensed into the final format of the SeCore CDx HLA Sequencing System. The final step in the process is Quality Control testing of the kit configuration prior to release.

In addition, the release process for the uTYPE CDx HLA Sequence Analysis Software can be found in Figure 6 in *009_SeCore CDx Device Description and Principles of Operation*.

Additional detail on manufacturing flowcharts can also be found in *012_SeCore CDx Manufacturing Flowchart.*

1.3 Principal of Test Procedure

The SBT test method consists of 1) DNA amplification via PCR and 2) DNA sequencing via Sanger sequencing technology and 3) Data Analysis

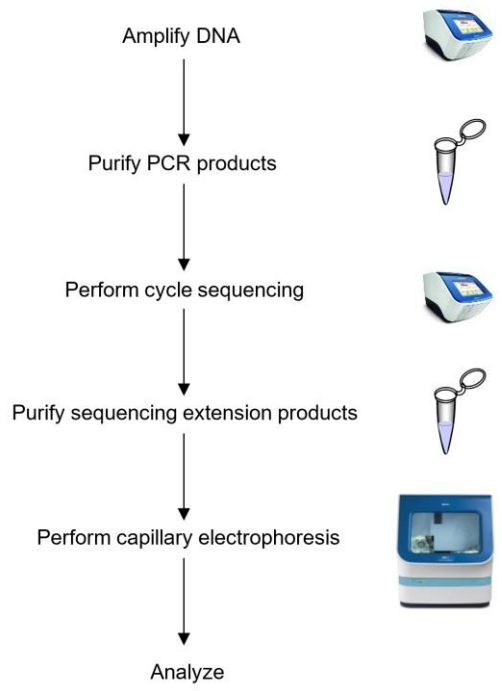
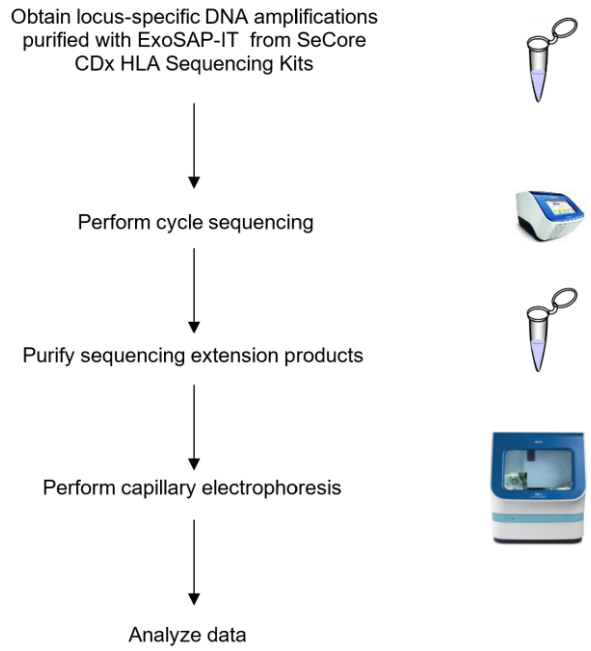
1. Amplification
   The DNA to be examined is extracted and purified from whole blood specimens. The SeCore CDx HLA Sequencing System process begins with the amplification of the target locus by combining Amplification Mix, FastStart™ Taq DNA Polymerase, and sample genomic DNA. Amplification of the target locus is accomplished using Polymerase Chain Reaction (PCR). During PCR amplification denatured single stranded DNA is hybridized to specifically designed oligonucleotide primers which only allow amplification of specific alleles or groups of alleles. New strands of target DNA sequences are synthesized by a heat-resistant enzyme (Taq polymerase) through utilization of a pool of deoxyribonucleotide triphosphates (dNTP's). The typing method is based on the principle that a matched primer will be more efficiently used in PCR than a primer with one or more mismatches. The specificity is derived from matching the terminal 3' nucleotide of the primers with the target DNA sequence. Taq DNA polymerase will only extend 3' matched primers due to its lack of 3' to 5' exonucleolytic proofreading activity. The effectiveness of the PCR process is checked by passing a portion of the reaction through an agarose gel to separate the reaction products. The success of the PCR reaction can be gauged by the presence or absence of bands of appropriate size when the gel is visualized under UV light.

2. Sequencing
   Once amplification is complete, the remaining amplified DNA product is treated with an enzyme cocktail consisting of exonuclease I and shrimp alkaline phosphatase (ExoSAP-IT™). This process is done prior to sequencing and its purpose is to degrade the unincorporated primers and hydrolyze unused dNTPs. The purified amplicon product undergoes fluorescence-based cycle sequencing in which fluorescently labeled dideoxynucleotides (BigDye™ Terminators) are incorporated into the 3' end of the amplified chain. BigDye Terminator Sanger Sequencing Chemistry carries two dyes, one a donor, the other an acceptor. The donor dye efficiently collects laser light and transfers it to one of four different acceptor dyes. The final reaction is purified using ethanol precipitation and resuspended in formamide to maintain DNA in the denatured state. The resultant DNA product is loaded onto the 3500 Dx / 3500xL Dx Genetic Analyzer CS2 and is scanned by capillary electrophoresis which produces an electropherogram. Sample files generated (.ab1) from the instrument are used by the uTYPE CDx HLA Sequence Analysis Software to match the sequencing results to known HLA allele sequences.

3. Data Analysis
uTYPE CDx HLA Sequence Analysis Software evaluates sequencing data files (.ab1) and generates HLA typing results. uTYPE CDx HLA Sequence Analysis Software is used to specifically interpret the output file from the 3500Dx / 3500xL Dx Genetic Analyzer CS2 by matching the sample sequencing results to the known HLA sequences. uTYPE CDx HLA Sequence Analysis Software works by loading sequence data from the 3500 Dx / 3500xL Dx Genetic Analyzer CS2 sample file (.ab1 files) to align the forward and the reverse sequencing data. The software then matches the sequence to known HLA allele sequences listed in the IMGT (ImMunoGeneTics) histocompatibility database used by HLA clinicians. One Lambda, Inc. has a process for analyzing quarterly database updates before they are distributed to uTYPE CDx HLA Sequence Analysis Software users. The output of the software is a report that indicates detected HLA alleles.

Analysis with the uTYPE CDx HLA Sequence Analysis Software will also determine if ambiguities exist within the initial sequencing results. Depending on the allele pairs obtained, ambiguities can be resolved by testing purified PCR products with SeCore CDx HLA GSSP (Group Specific Sequencing Primer) kits. The SeCore CDx GSSP Kit functions exactly the same as the locus specific sequencing mixture but is designed to target a specific allele or group of alleles within the target locus. To resolve ambiguity in initial test results, GSSPs only sequence specified alleles while excluding all other alleles within that locus. The SeCore CDx GSSP Kit provides users with a method for resolving ambiguities in initial sequencing data. Should further ambiguity resolution be required, the uTYPE HLA CDx Sequence Analysis Software provides the user with specific methods which allow alternative approaches to HLA allele reporting and ambiguity resolution. The output of the uTYPE CDx HLA Sequence Analysis Software is a report that indicates detected HLA alleles.

Figure 2: SeCore CDx HLA Sequencing System Workflow

SeCore CDx HLA Sequencing System Workflow	SeCore CDx HLA GSSP Kits Workflow
	

The detailed description of testing procedures and data analysis is provided in instructions for use for the SeCore CDx HLA Sequencing System

1.4 HLA Ambiguity Resolution Methods

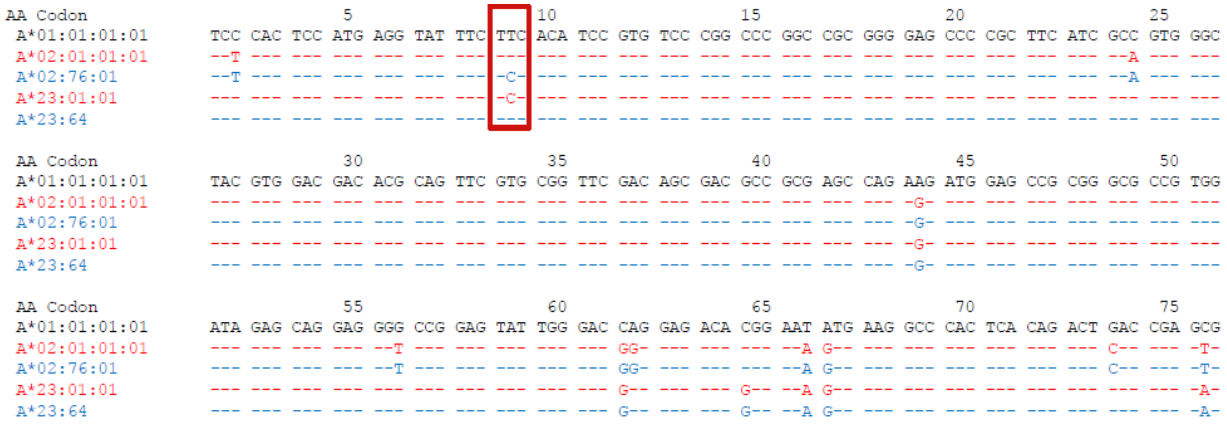
The SeCore CDx HLA Sequencing System has built-in mechanisms to resolve the majority of ambiguous HLA typing results. In most cases, the device will report the detected HLA allele subtypes with no ambiguity in the test result. In this case, HLA subtypes can be reported directly.

In certain situations, sequencing may generate an ambiguous genotype. This occurs when sequencing data can be interpreted as more than one potential combination of alleles in a sample. Not all HLA genes have 100% of the gene sequence published (see CIWD HLA database) and if the sequencing results match alleles with differences in unpublished regions, they may lead to ambiguous results.

For example, the SeCore CDx HLA Sequencing System sequences HLA-A locus exons 1-5 but does not include introns. As a result, intronic differences between alleles or mismatches outside the sequenced range will be listed as potential matches because it is not possible to rule out one potential allele variant from another potential allele variant.

Genotypic ambiguities or phase ambiguities (see Figure 3) result when phasing cannot be established between polymorphic positions and allele pairs cannot be said to belong together on one gene with certainty.

Figure 3: Example of an Ambiguous Genotype



Partial sequence of exon 2 illustrates the fact that a symmetrical T/C polymorphism between the 2 possible pairs of alleles (red box) results in an ambiguity that cannot be resolved by sequencing. The two possible genotypes are either A*02:01:01/A*23:01:01 (in red) or A*02:76:01/A*23:64 (in blue).

In instances where sequencing results cannot be fully resolved and remain ambiguous, the following methods will be employed:

1. If the allele pair does not contain an inclusion allele or does contain an exclusion allele, no further action will be taken as the subject will be deemed negative and will not receive the therapy.
2. If an inclusion allele in the pair is fully resolved and no exclusion allele is detected, no further action will be taken. Subject will be deemed positive.
3. If an exclusion allele in the allele pair is detected and fully resolved, no further action will be taken. Subject will be deemed negative.
4. If the detected alleles remain ambiguous but are resolved at the G-group[1] level (i.e., A*02:01:01G), the G-group will be reported. Results would be considered HLA-eligible if the G-group contains any target (inclusion) allele (e.g., A*02:01) and HLA-ineligible if the G-group either does not include any target allele or contains an exclusion allele (e.g., A*02:05).
5. If alleles remain ambiguous and are not part of an established G-group, ambiguities will be resolved through analysis of relative probabilities of ambiguous allele pairs. In this case, population frequencies of specific alleles and allele pairs would be collected from published sources (such as the CIWD and/or NMDP databases) to allow for ambiguities with rare genotypes to be resolved. In this method, an allele pair with ≥99% probability would be considered the resolved result and would be reported by the user.

For additional details on results interpretation, ambiguity resolution methods and therapeutic eligibility determinations, please refer the uTYPE CDx HLA Sequence Analysis Software User Manual.

[1] A G-group is a method for reporting ambiguous HLA allele strings. This method groups alleles with identical nucleotide sequences across the exon encoding the peptide binding domains (exon 2 and 3 for HLA Class I) into one allele code (e.g.., A*02:01:01G).

1.5 Results Interpretation

The uTYPE CDx HLA Sequence Analysis Software is intended to interpret and match sequencing data generated with the SeCore CDx HLA Sequencing System and the Applied Biosystems 3500 Dx /3500xL Dx Genetic Analyzer CS2 with the 3500 Dx Series Data Collection Software. The software works by loading sequence data from the 3500 Dx / 3500xl Dx Genetic Analyzer CS2 sample file to align the forward and the reverse sequencing results from the SeCore CDx HLA Sequencing System. uTYPE CDx software then matches the generated sequence to known HLA allele sequences listed in the IMGT (International lmMunoGeneTics) histocompatibility database. The output of the uTYPE CDx HLA Sequence Analysis Software is a report that indicates detected HLA alleles.

Analysis with the uTYPE CDx HLA Software will also determine if ambiguities exist within the initial sequencing results. Depending on the allele pairs obtained, ambiguities can be resolved by testing purified PCR products with GSSPs. The SeCore CDx HLA GSSP Kit functions exactly the same as the locus specific sequencing mixture but is designed to target a specific allele or group of alleles within the target locus. To resolve ambiguity in initial test results, GSSPs sequence specified alleles while excluding all other alleles within that locus. This provides users an integrated method for resolving ambiguities in initial sequencing data.

Afami-cel requires subjects to be 1) positive (1 copy or 2 copies) for any of the inclusion alleles HLA-A*02:01, HLA A*02:02, HLA-A*02:03 or HLA-A*02:06 and negative for the exclusion allele HLA-A*02:05 to be considered eligible to receive the therapeutic. HLA-A*02 alleles having the same protein sequence in the peptide binding domains (P-group) will also be included.

Biomarker negative subjects will 1) not have the HLA-A*02: 01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 alleles detected or 2) have HLA-A*02:05 detected regardless of the second HLA-A allele.

A summary table of the positive and negative results interpretation for the afami-cel therapy have been provided in Table 3.

Table 3: Interpretation of HLA Eligibility for afami-cel

HLA-A Typing*	Screening Result
A*02:01/A*XX:XX	HLA-eligible
A*02:02/A*XX:XX	
A*02:03/A*XX:XX	
A*02:06/A*XX:XX	
A*02:05/A*02:XX**	HLA-ineligible
A*02:XX/A*XX:XX	
A*XX:XX/A*XX:XX	

*Typing fields denoted with "XX" indicate that any possible allele combination in that field.
**The allele combination HLA-A*02:05/A*02:01(or any other inclusion allele) would be considered ineligible due to the presence of the A*02:05 allele.

1.6 Physical Characteristics

A complete summary of the physical characteristics for the device can be found in the attached device specification (refer to *010_SeCore CDx Device Specification*) and product bill of materials (Refer to *011_SeCore CDx Bill of Materials*).

Table 4: Summary of Physical and Chemical Characteristics

Component Name (Catalog)	Ingredients and Composition	Suggested Working Dilution	Volume Per Test	# of Tests Per Package
Amplification Mixture (STS017)	Ultra-Pure Water 10X PCR Buffer 25mM Magnesium Chloride Primers dNTP's DMSO	As provided	19.8µl	25
FastStart™ Taq DNA Polymerase (STS012-2)	Taq DNA Polymerase 5000 units/mL	As provided	0.2µl	25

Component Name (Catalog)	Ingredients and Composition	Suggested Working Dilution	Volume Per Test	# of Tests Per Package
Sequencing Mixtures (STSXXX XXX=107, 108, 109, 110, 019, 020, 021, 022, 023, 024)	Ultra-Pure Water Primers BigDye Terminators BigDye Dilution Buffer	As Provided	8µl	25
ExoSAP-IT (STS016-1)	Exonuclease Recombinant Shrimp Alkaline Phosphatase	As Provided	4µl	25
Sequencing PPT Buffer (STS-015-3)	Ultra-Pure Water EDTA 3.0M Na_2OAc	As provided	2µl	25

2. Intended Use and Indications for Use

The SeCore CDx HLA Sequencing System is intended for the detection of human leukocyte antigen A-locus (HLA-A) alleles using genomic DNA isolated from whole blood samples. The device is intended to be used as a companion diagnostic (CDx) to aid in the selection of patients who may benefit from treatment or are likely to be at increased risk for serious adverse reactions because of treatment with therapies listed in the table below when used in accordance with approved therapeutic labeling.

Table 5: Proposed Indications for Use

Indication(s)	HLA Target Allele(s)	Therapy
Unresectable or Metastatic Uveal Melanoma	Eligible allele: HLA-A*02:01	KIMMTRAK® (tebentafusp-tebn)
Unresectable or Metastatic Synovial Sarcoma in Patients who have Received Prior Systemic Therapy	Eligible alleles: HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles Exclusion alleles: HLA-A*02:05 and its P-group alleles	TECELRA® (afamitresgene autoleucel)

2.1 Patient Population

SS is a rare type of chromosomal translocation positive soft-tissue sarcoma (STS) that represents approximately 5% to 10% of all STS diagnoses in the overall population. SS is a serious, life-threatening disease with an estimated annual incidence of 800 to 1,000 cases in the United States and a 5-year overall and cancer-specific survival of approximately 52% and 66%, respectively. Outcomes are particularly poor in the metastatic setting with a 5-year overall survival (OS) rate of 15% after the date of diagnosis of the metastasis.

For many types of advanced or metastatic STS, including SS, cytotoxic therapies remain the cornerstone of first-line treatment. Standard first-line chemotherapy for metastatic disease typically involves the administration of single-agent doxorubicin or doxorubicin in combination with ifosfamide. Beyond first-line, real-world evidence from large volume SS centers in the US indicates that there is no standard-of-care (SoC) with only approximately 12% of patients receiving licensed second-line metastatic therapies. Patients who relapse after first-line therapy have very few treatment options and poor outcomes, with time-to-next-treatment and overall survival progressively worsening with each subsequent line of treatment. In patients who relapse after first-line therapy, a median survival of around 12 months is estimated after second-line therapy. There is clearly a high unmet medical need for more effective therapies in patients with SS who have progressed after first-line systemic treatment.

SS was selected as an indication for afami-cel clinical development based on the high frequency of MAGE-A4 expression in this tumor indication. Based on Adaptimmune screening data in SS, 67% of HLA-A*02 positive patients have MAGE-A4 expressing tumors.

Currently, the SeCore CDx HLA Sequencing System discriminates HLA-A*02:01 alleles in patients with unresectable or metastatic uveal melanoma for treatment with KIMMTRAK® (tebentafusp-tebn). The device that is subject of the premarket notification submission is identical to the De Novo granted device previously cleared by FDA on November 28, 2022 (see BR220737) and has the same form, fit, and function with the exception of expanded indication for use in the SS patient population and associated target alleles for use with afami-cel. To support the expanded indication for use in the SS patient population, an analytical accuracy study was carried out with SS patient samples to ensure that the SeCore CDx HLA Sequencing System can accurately and provide HLA-A screening data in the inclusion/exclusion criteria for the safe and effective use in potential treatment with afami-cel. (see 018_SeCore CDx Analytical Validation for Afami-cel)

HLA genotyping is one part of the eligibility criteria to select subjects to receive afami-cel and eligible subjects must have a specific HLA genotype. Subjects positive for HLA-

A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles and do not carry HLA-A*02:05 and associated P-group alleles are suitable to receive treatment with afami-cel.

Afami-cel is a genetically modified autologous T-cell immunotherapy consisting of CD4 and CD8 positive T-cells that express an enhanced-affinity TCR specific for melanoma-associated antigen A4 (MAGE-A4). MAGE-A4 is an intracellular testis antigen that has restricted expression in normal tissues but is expressed across a range of solid tumors at varying frequencies. In vitro, antigen-specific activation of afami-cel, via TCR-peptide HLA-A*02 complex, results in T-cell proliferation, cytokine secretion, and killing of MAGE-A4/HLA-A*02 expressing cancer cells.

For additional details, refer to Adaptimmune' s afami-cel Biologics License Application BL 125789.

3. Proposed Predicate Device

The device that is subject of the premarket notification submission has the same technological characteristics as the predicate device, the De Novo granted device previously cleared by FDA on November 28, 2022 (see BR220737).

A summary of the technological characteristics is as follows:

Table 6: Comparison with Proposed Predicate Device

	Predicate Device (BR220737)	**New Device (BK# Pending)**
Device Name	SeCore™ CDx HLA Sequencing System	Same
Submission Number	BR220737	Pending
Regulation Number	21 CFR 866.5960	Same
Regulation Name	Human leukocyte antigen typing companion diagnostic test	Same
Classification	Class II	Same

<table>
<tr><th></th><th>Predicate Device

(BR220737)</th><th>New Device

(BK# Pending)</th></tr>
<tr><td>Product Code</td><td>QUK</td><td>Same</td></tr>
<tr><td>Intended Use</td><td>The SeCore CDx HLA Sequencing System is intended for the detection of human leukocyte antigen A-locus (HLA-A) alleles using genomic DNA isolated from whole blood samples. The device is intended to be used as a companion diagnostic (CDx) to aid in the selection of HLA-A*02:01 positive patients with unresectable or metastatic uveal melanoma who may benefit from treatment with KIMMTRAK® (tebentafusp-tebn) when used in accordance with approved therapeutic labeling.</td><td>The SeCore CDx HLA Sequencing System is intended for the detection of human leukocyte antigen A-locus (HLA-A) alleles using genomic DNA isolated from whole blood samples. The device is intended to be used as a companion diagnostic (CDx) to aid in the selection subjects who may benefit from treatments listed below when used in accordance with approved therapeutic labeling:
<table>
<tr><th>Indication(s)</th><th>HLA Target Allele(s)</th><th>Therapy</th></tr>
<tr><td>Unresectable or metastatic Uveal Melanoma</td><td>Eligible allele: HLA-A*02:01</td><td>KIMMTRAK® (tebentafusp-tebn)</td></tr>
<tr><td>Unresectable or Metastatic Synovial Sarcoma in Patients who have Received Prior Systemic Therapy</td><td>Eligible alleles: HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles

Exclusion alleles: HLA-A*02:05 and its P-group alleles</td><td>TECELRA® (afamitresgene autoleucel)</td></tr>
</table></td></tr>
<tr><td>Indications for Use</td><td>For use in the Uveal Melanoma patient population.</td><td>For use in the unresectable or metastatic uveal melanoma and the unresectable or metastatic synovial sarcoma patient populations.</td></tr>
<tr><td>Assay Method</td><td>Sequence Based Typing</td><td>Same</td></tr>
<tr><td>Reactive Ingredient</td><td>Genomic DNA</td><td>Same</td></tr>
<tr><td>Specimen Type(s)</td><td>Whole Blood</td><td>Same</td></tr>
<tr><td>Sample Type(s)</td><td>Purified DNA</td><td>Same</td></tr>
<tr><td>Detection Reagents</td><td>Fluorescent emission detection from BigDye™ Terminators</td><td>Same</td></tr>
</table>

	Predicate Device (BR220737)	New Device (BK# Pending)
Software Technology	Uses personal computer. Operates with a Windows 10 operating system	Same
Software Main Components	uTYPE CDx HLA Sequence Analysis Software	Same
Instrumentation	DNA Amplification: Veriti™ Dx 96-Well Thermal Cycler Model 9912 with 0.2–mL sample wells (Class I Device) Capillary electrophoresis: Applied Biosystems 3500 Dx /3500 xL Dx Genetic Analyzer CS2 (Class 2 Device, 510(k)-cleared BK110039)	Same

4. Nonclinical Studies

The SeCore CDx HLA Sequencing System has well established analytical performance characteristics from analytical studies conducted for 510(k)-clearance (refer to BK110038). As previously agreed by the agency during pre-submissions BQ # 180281 and BQ # 210660, existing nonclinical studies previously conducted for the SeCore HLA Sequencing System will be used to support analytical performance characteristics for the proposed companion diagnostic device with expanded indication in the SS population for use with afami-cel (refer to BK110038 for analytical performance).

Two additional studies have been completed to support the SeCore CDx HLA Sequencing System for use as a companion diagnostic:

1. Analytical Accuracy
    a. Purpose: To ensure device is accurate within the target population and effectively discriminate the required target allele (HLA-A*02:01).

b. Purpose: To ensure device is accurate within the target population and effectively discriminate the required target alleles (HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles, excluding HLA-A*02:05 and its P-group alleles).

The studies both include samples from the target intended use population and well-characterized reference samples to establish accuracy for the device.

2. Clinical Validity

a. Purpose: To establish a clinical benefit and clinically validate the use of the device as part of eligibility determinations for clinical trials conducted with the target therapeutic.

Refer to BLA # 761228 (KIMMTRAK) and BL 125789 (TECELRA).

The objective of the additional submitted studies is to build on the existing analytical performance of the SeCore CDx HLA Sequencing System (BR220737) and to clinically validate the SeCore CDx HLA Sequencing System for use as a companion diagnostic.

4.1 Analytical Accuracy Studies:

An accuracy study supplementing existing data was performed on samples from the intended target population and well-characterized reference samples to ensure that the device can accurately detect the target inclusion and exclusion alleles.

4.1.1 Detection of HLA-A*02:01 (KIMMTRAK)

Study Overview The study consisted of 33 samples collected from individuals with metastatic or unresectable uveal melanoma and 72 well-characterized reference samples from the UCLA reference panel. A total of 105 samples were included in the study. Accuracy study samples were evaluated using the SeCore CDx HLA Sequencing System and compared to established reference typing to generate percent concordance measurements. For samples without established reference typing, typing results were compared to confirmatory results collected with a gold standard NGS test (the CE-marked AllType FASTplex NGS 11 Loci Flex Kit). (See BR220737)

4.1.2 Detection of HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles, excluding HLA-A*02:05 and its P-group alleles (Afami-cel)

Study Overview The study consisted of 6 samples collected from individuals with Unresectable or Metastatic Synovial Sarcoma and 64 well-characterized reference samples from the UCLA, IHWG, and internal reference panel. A total of 70 samples

were included in the study. Accuracy study samples were evaluated using the SeCore HLA Sequencing System and compared to established reference typing or published reference genotype from IHWG or UCLA to generate percent concordance measurements. For samples without established reference typing, typing results were compared to confirmatory results collected with a gold standard NGS test (AllType™ NGS 11-Loci Amplification Kit).

4.1.3 Data Analysis

Data Analysis was conducted by calculating overall percent agreement (OPA), positive percent agreement (PPA) and negative percent agreement (NPA). For the concordance analysis, the lower-bound (LB) of a one-sided 95% confidence interval (CI) was required to be at least 0.95 for measurements that met the minimum sampling requirement. If a sufficient number of positive or negative samples could not be evaluated, concordance measurements were required to demonstrate 100% agreement by point estimate.

4.1.4 Study Results and Conclusions

KIMMTRAK

The SeCore CDx HLA Sequencing System detected and correctly identified the HLA-A*02:01 allele in patients with metastatic or unresectable uveal melanoma. The lower-bound (LB) of the 95% one-sided confidence interval was calculated to be 97.2% using the Clopper-Pearson method and 97.5% using the Wilson method. (see BR220737 for additional details).

Afami-cel

The SeCore CDx HLA Sequencing System detected and correctly identified HLA-A*02 alleles including HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles, excluding HLA-A*02:05 and its P-group alleles in a total of 37 samples. The remaining 33 samples were correctly identified with the absence of the target inclusion or exclusion allele.

Two IHWG published reference samples used in the accuracy study, FH53 and FH75, were originally found to be discordant with the SeCore CDx HLA Sequencing System results. An investigation discovered that the published results sequenced only exons 2 and 3 for FH53. Differences in additional exons (namely exon 4) caused discordant results between the published typing and the SeCore CDx assay. Additionally, for FH75, an article published in 2015 (Wittig, 2015) noted the same erroneously published HLA typing result as seen during the accuracy study testing. The NGS reference testing provided the same results as the SeCore CDx device for both samples suggesting that the published reference sample typing results were

incorrect. Currently, IHWG has corrected the published genotype results and these can be found on their website (https://www.fredhutch.org/content/dam/www/research/divisions/clinical-research-division/IHWG/available-cells-dna-hla-types.pdf). In consideration of the two inaccurately published HLA typing results, a 100% overall percent agreement (OPA) was demonstrated for the device.

The overall concordance percentage for the accuracy study was 100% by point estimate, with all typing results generated from the SeCore CDx HLA Sequencing System matching the expected sample reference typing. The lower-bound (LB) of the 95% one-sided confidence interval was calculated to be 95.8% using the Clopper-Pearson method and 96.3% using the Wilson method.

The PPA and NPA for the accuracy study was calculated to be 100% by point estimate. All samples where HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles, excluding HLA-A*02:05 and its P-group alleles were detected by the SeCore CDx HLA Sequencing System matched expected reference typing. The total number of positive samples and negative samples did not meet the minimum sampling requirements to calculate a 95% one-sided confidence interval, therefore results were assessed via point estimate. All samples where HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles, excluding HLA-A*02:05 and its P-group alleles were not detected by the SeCore CDx HLA Sequencing System matched the expected sample reference typing. The SeCore CDx HLA Sequencing System met expected performance requirements for overall concordance, NPA and PPA. The results demonstrate that the system can accurately identify and define the target alleles, HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles, excluding HLA-A*02:05 and its P-group alleles in patients with unresectable or metastatic synovial sarcoma.

5. Clinical Studies

An evaluation of the performance of the Life Technologies SeCore™, uTYPE® and 3500xL Dx System, comprising of SeCore® Sequencing Kits tested using the Applied Biosystems 3500 Dx / 3500xL Dx Genetic Analyzer CS2 and 3500 Dx Series Data Collection Software with uTYPE® Dx HLA Sequence Analysis Software, compared to the predicate device SSP UniTray® with UniMatch® Plus Interpretation Software, was conducted at three sites in the United States. The study objective was to determine if the concordance rate was at least 0.95. The corresponding statistical hypotheses for each locus of the 5 loci are H0: $r \leq 0.95$ and Ha: $r > 0.95$. A one-sided type I error rate of $\alpha = 0.05$ and a statistical power of 80% at a true concordance rate of 0.98 was used for the calculated sample size. Based on Fisher's exact test, a sample size of 260 (split between the three sites) was needed. While a sample

size of 260 was calculated to ensure at least 80% power, the total sample size was increased to 300 (total across all sites). This was to ensure adequate power (approximately 85%) for the statistical analyses. For the primary analyses, the confidence intervals were

not adjusted for multiplicity. However, an additional pre-specified analysis was conducted to investigate the robustness of the results after adjusting the confidence intervals for multiplicity. Each laboratory selected 100 DNA samples per loci for testing. Samples were randomly selected.

Table below summarizes the comparative study results.

Table 7: Concordance Results

SeCore® Kit	Concordance[1]	90% Confidence Interval[2]	Success[3]
A Locus	100.0% (299/299)	(99.00%, 100.0%)	Yes

[1] Concordance is reported as Percent (Number concordant/Number of Samples).
[2] Confidence interval calculated by the Clopper-Pearson method.
[3] Success is determined by a lower bound on the 90% confidence interval greater than 0.95.

The results of the clinical studies performed with the SeCore™ HLA Sequencing System met the acceptance criteria of 95% concordance with 90% confidence for all Class I and Class II loci (A, B, C, DRB1, DRB3/4/5, DQB1, DPB1) demonstrating acceptable agreement to the predicate device, Life Technologies' SSP UniTray with UniMatch Plus interpretation software.

All samples tested in the predicate device comparison study demonstrated an overall concordance of 99.5% with a 90% confidence between the two methods. For all SeCore™ kits, the lower 90% confidence limit is higher than 0.95, demonstrating that the 95% concordance primary endpoint of the Clinical study was achieved. (see BK11038 for additional details)

Additional companion diagnostics clinical trials were conducted to support the use of the SeCore CDx HLA Sequencing System to aid in the selection of patients who may benefit from treatment with associated therapies.

5.1 Therapy Specific Clinical Studies

5.1.1 KIMMTRAK Study Overview (IMCgp100-202)

Clinical studies were conducted to establish the clinical benefit and effectiveness of using the SeCore CDx HLA Sequencing System to identify HLA-A*02:01 in patients with unresectable or metastatic UM.

The SeCore CDx HLA Sequencing System was used to provide a determination of HLA-A*02:01 positivity in patients during clinical trials for KIMMTRAK as part of the clinical eligibility criteria for the studies (see BR220737 for additional details).

5.1.2 Afami-cel Study Overview (ADP-0044–001, ADP-0044–001R, and ADP-0044-002)

5.1.2.1 Overview

Synovial sarcoma is a rare and serious life-threatening disease associated with poor outcomes in the refractory/metastatic (advanced) setting. In the second-line metastatic setting and beyond, licensed therapies for synovial sarcoma are associated with low response rates (ORRs under 18%) and no improvement in OS, which highlights the high unmet medical need in this patient population.

Clinical studies were conducted and sponsored by Adaptimmune, LLC and are being utilized to support drug approval for afami-cel (refer to BL 125789). A rolling BLA submission for afami-cel was completed by Adaptimmune, LLC, on December 5, 2023 (BL 125789). FDA's Filing Notification was received January 31, 2024, confirming Priority Review and a review goal date of August 4, 2024. In Adaptimmune's present BLA, primary evidence to support the indication for afami-cel in advanced SS is provided by the ADP-0044-002 phase 2 study (Cohort 1).

The SeCore CDx HLA Sequencing system, when used as a CDx to screen patients for HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles, excluding HLA-A*02:05 and its P-group alleles, provides critical HLA allele data to support the safe and effective use of the investigational therapy, afami-cel, in the treatment of unresectable or metastatic SS.

5.1.2.2 Specimen Samples

All clinical efficacy data was generated from whole blood specimens collected from eligible participants in the clinical trials for afami-cel. During the ADP-0044-002 study, a total of 12 Cohort 1 subjects were tested with buccal swabs. Among them, a total of 4 subjects were considered HLA-eligible (positive for HLA-A*02:01, 02:02, 02:03 or 02:06 and their P-group alleles and negative for HLA-A*02:05 and its P-group alleles) and 3 of these subjects were considered study eligible (HLA-A*02 detected and MAGE-A4 positive). All 3 samples that were HLA eligible had their HLA genotype confirmed using a blood sample for subsequent enrollment into the interventional clinical study for afami-cel. All subjects who were enrolled in the interventional clinical study for afami-cel with HLA alleles pre-screened with buccal swabs had their HLA typing results confirmed through screening of blood samples.

In addition to cohort 1 of ADP-0044-002, 25 buccal swab samples with matched blood samples have been collected for Cohort 2 of the ADP-0044-002 trial (N=7) and other

Adaptimmune sponsored clinical studies (N=18) during subject pre-screening. A total of 28 subjects have been tested with the CTA using both buccal swab and blood samples across these studies. HLA typing results collected with the CTA were 100% concordant between buccal swab and blood samples.

Buccal swabs are not intended to be used in a commercial setting and will not be a specimen type in the labeling for the SeCore CDx HLA Sequencing System. As a result, OLI and Adaptimmune will exclude subject data that utilized buccal swab specimens during pre-screening that were not verified with blood samples from the device submission as there is no impact to the clinical efficacy measurement ((004_SeCore CDx HLA Sequencing System_Pre-sub Teleconference Meeting Minutes_BQ230984.2). All clinical efficacy data presented in the 510(k) for the SeCore CDx HLA Sequencing System is represented with only blood samples which is the specimen type validated for use and detailed in the commercial device labeling. Descriptive statistics for the resulting data can be found in the SeCore CDx HLA Sequencing System Clinical Summary Report, *019_SeCore CDx HLA Sequencing System Clinical Summary Report – Adaptimmune Afami-cel*.

5.1.2.3 Clinical Endpoints

The clinical endpoints for the SeCore CDx HLA Screening System include providing HLA typing data and identifying synovial sarcoma patients that are positive for HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles, excluding HLA-A*02:05 and its P-group alleles for clinical study ADP-0044–002. The primary endpoint for afami-cel is based on overall response rate (ORR) for confirmed tumor responses per RECIST by independent review. Additional secondary endpoints were time to response (TTR), Duration of response (DOR), best overall response (BOR), progression-free survival (PFS) and overall survival (OS). All drug efficacy measurements were calculated using specimens from whole blood specimens.

5.1.2.4 Efficacy Conclusions

Synovial sarcoma is a rare and serious life-threatening disease associated with poor outcomes in the refractory/metastatic (advanced) setting. In the second-line metastatic setting and beyond, licensed therapies for synovial sarcoma are associated with low response rates (ORRs under 18%) and no improvement in OS, which highlights the high unmet medical need in this subject population.

ADP-0044–002 Cohort 1 forms the primary basis of efficacy of afami-cel in subjects with advanced SS who have received prior systemic therapy. The major efficacy outcomes was overall response rate (ORR) according to RECIST v1.1 evaluated by independent review and supported by duration of response (DOR). The ORR was 43.2% (95% CI: 28.4, 59.0) by Independent review with a median DOR of 6.0 months (95% CI: 4.6, NR) by independent review.

The ORR results are presented in the table below:

Table 8: Overall Response Rate, ADP-0044-002 Cohort 1

Parameter	mITT, n=44
Best overall response, n (%)	
Complete response	2 (4.5)
Partial response	17 (38.6)
Stable disease	20 (45.5)
Progressive disease	5 (11.4)
Overall response rate	
Complete response + partial response, n (%)	19 (43.2)
95% CI	(28.4, 59.0)

Note: Modified ITT Population (mITT)

The efficacy data presented provides substantial evidence of the effectiveness of afami-cel through demonstration of a clinically meaningful ORR, supported by DOR, according to independent review in patients with unresectable or metastatic synovial sarcoma who are positive for HLA-A*02 (HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles, excluding HLA-A*02:05 and its P-group alleles) and whose tumor expresses the MAGE-A4 antigen. In the setting of this serious and life-threatening illness with limited treatment options, these results represent a direct clinical benefit for patients with this rare cancer.

For comprehensive details on the clinical efficacy, refer to BL 125789

5.1.2.5 Clinical Benefit of the SeCore CDx HLA Sequencing System

The SeCore CDx HLA Sequencing system, when used as a CDx, provided critical HLA allele data to support the safe and effective use of KIMMTRAK in the treatment of unresectable or metastatic UM and use of Afami-cel in the treatment of unresectable or metastatic synovial sarcoma.

For comprehensive details on clinical studies, refer to BL 125789, BR220737 and *020_SeCore CDx HLA Sequencing System Clinical Summary Report*.

6. Software & Cybersecurity

One Lambda, Inc. manages cybersecurity during product design and development (TDX-SOP-0022) through post market surveillance (TDX-SOP-0089). OLI's software development lifecycle (TDX-SOP-0047) includes cybersecurity inputs from design and

development and cybersecurity inputs from risk control. These design and risk control input requirements are included in the software and in validated software updates or patches which occur throughout the product lifecycle assuring continued safety and effectiveness.

The design and development process as part of design controls (TDX-SOP-0022), addresses cybersecurity risks through software design input requirements. Any identified applicable requirements are included as part of the software design documentation (SDS) and software risk control measures. Cybersecurity risk control measures are documented in the product Failure Mode and Effect Analysis (FMEA) and the product Risk Management Review Report. The OLI software development lifecycle includes an initial cybersecurity design assessment, penetration testing, and continued security assessments during software risk management reviews.

The post market surveillance (PMS) process includes monitoring the cybersecurity risk for the product during its lifecycle. Elements of the PMS include assessing changes in technology and regulations, reviewing risks from similar products in the field, and analyzing customer complaints. Where applicable, outputs from the PMS process feed into software lifecycle change management by triggering validated software updates or patches to assure the continued safety and effectiveness of the system.

7. Conclusion

The SeCore CDx can effectively discriminate HLA-A*02:01, HLA-A*02:02, HLA-A*02:03 or HLA-A*02:06 and their P-group alleles as well as identify exclusion target alleles, HLA-A*02:05 and its P-group alleles. In addition to the results of nonclinical studies and clinical studies, analytical accuracy studies conducted in the original device 510(k) and De Novo granted BR220737 as well as the current proposed expanded indication in the SS population demonstrate that the SeCore CDx HLA Sequencing System performs as well as the legally marketed predicate device and can safely and effectively provide HLA-A screening data results for potential treatment with associated therapies.