510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

K182797

B. Purpose for Submission:

To obtain a substantial equivalence determination for the addition of Eravacycline at concentrations 0.008 – 16 µg/mL for testing non-fastidious Gram negative and Gram positive organisms on the Sensititre 18 – 24 hour MIC or Breakpoint Susceptibility System

C. Measurand:

Eravacycline 0.008 – 16 µg/mL

D. Type of Test:

Quantitative Antimicrobial Susceptibility Test (AST) growth-based detection

E. Applicant:

ThermoFisher Scientific

F. Proprietary and Established Names:

Sensititre 18 24 hour MIC or Breakpoint Susceptibility System with Eravacycline in the dilution range of 0.008 16 µg/mL

G. Regulatory Information:

1. Regulation section:

   866.1640 Antimicrobial Susceptibility Test Powder

2. Classification:

   Class II

3. Product code:

   JWY- Manual Antimicrobial Susceptibility Test Systems
   LRG- Instrument for Auto Reader and Instrumentation of Overnight Susceptibility Systems

LTT- Panels, Test, Susceptibility, Antimicrobial

4. Panel:

   83- Microbiology

H. Intended Use:

1. Intended use(s):

   The Sensititre MIC and Breakpoint Susceptibility system is an *in vitro* diagnostic product for clinical susceptibility testing of non-fastidious Gram negative isolates, comprising of *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and other non-*Enterobacteriaceae* and of non-fastidious Gram positive isolates, comprising of *Staphylococcus spp*., *Enterococcus spp.*, and Beta haemolytic *Streptococci* other than *S. pneumoniae*.

2. Indication(s) for use:

   The Sensititre 18 – 24 hour MIC or Breakpoint Susceptibility System is an *in vitro* diagnostic product for clinical susceptibility testing of non-fastidious isolates.

   This 510(k) is for Eravacycline in the dilution range 0.008 – 16 µg/mL for testing non-fastidious Gram negative and Gram positive organisms on the Senstitire 18 – 24 hour MIC panel.

   Eravacycline has been shown to be active both clinically and *in vitro* against the following organisms according to the FDA drug label:

   Gram negative bacteria
   Escherichia coli
   Klebsiella oxytoca
   Klebsiella pneumoniae
   Citrobacter freundii
   Enterobacter cloacae

   Gram positive bacteria
   Enterococcus faecalis
   Enterococcus faecium
   Staphylococcus aureus

   The following *in vitro* data are available, but their clinical significance is unknown:

   Gram negative bacteria
   Citrobacter koseri
   Klebsiella (*Enterobacter*) *aerogenes*

3. Special conditions for use statement(s):

For prescription use only

The following information is included in the limition section of the labeling:

Non-Fastidious Gram Negative Organisms:

- The performance of eravacycline with Gram negative organisms was performed using the AutoReader (OptiRead) and VIZION reading methods only. The use of an alternative reading method when testing eravacycline has not been evaluated.

- Studies of eravacycline were performed using the AIM autoinoculator. The use of an alternative inoculation system when testing eravacycline has not been evaluated.

- There were 47 Eravacycline non-susceptible *Enterobacteriaceae* isolates as determined by the reference method. Although MIC results were within essential agreement, five and six potential very major (vmj) discrepancies were observed with the VIZION and OptiRead, respectively, due to the lack of intermediate category. When the Sensititre MIC is at the breakpoint of 0.5 µg/mL, testing should be repeated using a reference/alternative testing method prior to reporting results for Eravacycline with *Enterobacter cloacae, E. coli, K. pneumoniae*, or *Citrobacter koseri* with VIZION and *Enterobacter cloacae, E. coli, K. pneumoniae, K. oxytoca,* or *Citrobacter koseri* with OptiRead.

- Resistance mechanism characterization was not available for all organisms at the time of comparative testing, and therefore the performance of the Sensititre Eravacycline is unknown for *Enterobacteriaceae* with efflux mediated by tet(A), and tet(B).

- The safety and efficacy of eravacycline in treating clinical infections due to bacteria other than *E. coli, K. pneumoniae, K. oxytoca, E. cloacae,* and *C. freundii* may or may not have been established in adequate and well-controlled clinical trials and the clinical significance of such susceptibility information in those instances is unknown.

Non-Fastidious Gram Positive Organisms (*Staphylococcus aureus, Enterococcus faecalis, E. faecium*):

- Studies of Eravacycline were performed using the AIM autoinoculator. The use of an alternative inoculation system when testing Eravacycline has not been evaluated.

- The performance of Eravacycline with *Staphylococcus aureus* (MRSA and MSSA), *Enterococcus faecalis*, and *Enterococcus faecium* was evaluated using

the AutoReader (OptiRead) and Vizion reading methods only. The use of an alternative reading method when testing Eravacycline has not been evaluated.

- There were 561 Eravacycline susceptible Gram positive (non-fastidious) isolates as determined by the reference method. Although within essential agreement, 39 and 24 potential major (maj) discrepancies were observed with the VIZION and OptiRead, respectively, due to the lack of an intermediate category. When the Sensititre MIC is at 0.12 µg/mL, the non-susceptible breakpoint, testing should be repeated using a reference/alternative testing method prior to reporting results for Eravacycline with *S. aureus, E. faecalis*, and *E. faecium* for the VIZION reading method and *S. aureus* with the OptiRead reading method.

- There were 41 Eravacycline non-susceptible Gram positive (non-fastidious) isolates as determined by the reference method. Although within essential agreement, four and five potential very major (vmj) discrepancies were observed with the VIZION and OptiRead, respectively, due to the lack of intermediate category. When the Sensititre MIC is at the breakpoint of 0.06 µg/mL, testing should be repeated using a reference/alternative testing method prior to reporting results for Eravacycline with Staphylococcus aureus with VIZION and with OptiRead.

- Resistance mechanism characterization was not available for all organisms at the time comparative testing, and therefore the performance of the Sensititre Eravacycline is unknown for non-fastidious Gram positive (*Staphylococcus aureus, Enterococcus faecalis,* and *Enterococcus faecium*) isolates with efflux mediated by tet(K) and ribosomal protection as encoded by tet(M).

- The safety and efficacy of eravacycline in treating clinical infections due to bacteria other than *Staphylococcus aureus, Enterococcus faecalis,* and *Enterococcus faecium* may or may not have been established in adequate and well-controlled clinical trials and the clinical significance of such susceptibility information in those instances is unknown.

4. Special instrument requirements:

   Sensititre AIM for device inoculation
   Sensititre VIZION or OptiRead for plate reading

I. Device Description:

Sensititre MIC Susceptibility plate MIC panels are multi-well plastic micro-titer plates, dosed with dried, stabilized antimicrobials. It is a miniaturized version of the classic broth dilution methods and can provide both qualitative and quantitative susceptibility results. After inoculation, plates are sealed with an adhesive seal, incubated at 34 – 36°C for 18 – 24 hours and examined for bacterial growth.

Antimicrobial susceptibility test results can be determined by reading of growth using the digital viewing device (VIZION) or automatically on an autoreader (OptiRead) using fluorescence.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   Sensititre 18-24 hour Susceptibility MIC Plates, Ceftazidime/avibactam

2. Predicate 510(k) number(s):

   K152774

3. Comparison with predicate:

Table 1: Comparison with Predicate Device

Similarities		
Item	**Device** Sensititre 18–24 Susceptibility System, Eravacycline (K182797)	**Predicate** Sensititre 18–24 Susceptibility System, Ceftazidime/avibactam (K152774)
Intended Use	The Sensititre MIC and Breakpoint Susceptibility System is an in vitro diagnostic product for clinical susceptibility testing of non-fastidious Gram negative isolates, comprising of *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and other non-*Enterobacteriaceae* and of non-fastidious Gram positive isolates, comprising of *Staphylococcus spp*., *Enterococcus spp*., and Beta haemolytic *Streptococci* other than *S. pneumoniae*	Same
Test Panel	96-well plate dosed with selected antimicrobial agents then dried	Same
Reading Methods	Results can be read by 1) the automated OptiRead, 2) the digital viewing VIZION device	Same
Incubation	18 – 24 hours	Same
Differences		
Drug	Eravacycline	Ceftazidime/Avibactam
Dilutions	0.008 – 16 µg/mL for Gram negative and Gram positive isolates	0.015/4 – 32/4 µg/mL for Gram negative isolates

Similarities		
Item	**Device** Sensititre 18–24 Susceptibility System, Eravacycline (K182797)	**Predicate** Sensititre 18–24 Susceptibility System, Ceftazidime/avibactam (K152774)
Results	Report results as Minimum Inhibitory Concentration (MIC) and interpretive criteria (S, --, --). Susceptible is the only interpretive category for Eravacycline	Report results as Minimum Inhibitory Concentration (MIC) and interpretive criteria (S, I, R)

K. Standard/Guidance Document Referenced (if applicable):

Guidance for Industry and FDA - Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems – August 28, 2009.

CLSI M100: Performance Standards for Antimicrobial Susceptibility Testing; 28th Edition, January 2018

CLSI M7: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically, 11th Edition, January 2018

L. Test Principle:

The Sensititre 18 - 24 hour MIC or Breakpoint Susceptibility System are multi-well plastic microtitre plates that contain doubled dilution of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read by the VIZION or by use of an automated reader (OptiRead).

The VIZION allows the panel image to be displayed on a touch screen directly from a video camera and allows the user to manually select MIC results. The Sensititre OptiRead utilizes fluorescence technology to read the microbroth dilution plates after 18 to 24 hours incubation. The technology involves the detection of bacterial growth by monitoring the activity of specific surface enzymes produced by the test organism. Growth is determined by generating a fluorescent product from a fluorogenic substrate. The substrate is prepared by conjugating a fluorescent compound to the specific enzyme substrates with a bond which prevents fluorescence. The enzymatic action of the bacterial surface enzymes on the substrate cleaves the bond releasing fluorescence. The amount of fluorescence detected is directly related to bacterial growth. The MIC is determined by observing the lowest dilution of antimicrobial agent that inhibits growth of the organism. The substrate can be added to the inoculum broth which is dispensed into the test plate at the same time as the test organism, or, the plates can be prepared with the substrate already added to each micro-well.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

   a. *Precision/Reproducibility:*

      Non-fastidious Gram Negative Organisms
      A reproducibility study was performed at four sites using 12 Gram negative organisms that included five *E. coli* isolates, four *Klebsiella pneumoniae* isolates, two isolates of *K. oxytoca*, and one *Enterobacter cloacae* isolate. The isolates were tested in triplicate over three different days for each reading method (i.e., VIZION and OptiRead) for a total of 432 data points for each.

      Non-fastidious Gram Positive Organisms
      A reproducibility study was performed at four sites using 13 Gram positive organisms that included five methicillin resistant *Staphylococcus aureus* (MRSA), five methicicllin susceptible *Staphylococcu aureus* (MSSA), one vancomycin resistant (VR) *Enterococcus faecalis,* one vancomycin susceptible (VS) *E. faecalis,* and one VR *E. faecium.* The isolates were tested in triplicate over three different days for each reading method (i.e., VIZION and OptiRead) for a total of 468 data points for each.

      The Sensititre AIM was used for plate inoculation. The mode MIC value was pre-determined and the reproducibility was calculated based on MIC values falling within ±1 dilution of the mode MIC value. All MIC results were on-scale by both reading methods. Reproducibility was greater than 95% for both the VIZION and the OptiRead methods. The results were acceptable.

   b. *Linearity/assay reportable range:*

      Not Applicable

   c. *Traceability, Stability, Expected values (controls, calibrators, or methods):*

      Non-fastidious Gram Negative Organisms
      The CLSI recommended QC strains, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were tested a sufficient number of times (i.e., at least 20/site) at each testing site.

      Non-fastidious Gram Positive Organisms
      The CLSI recommended QC strains, *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 were tested a sufficient number of times (i.e., at least 20/site) at each testing site.

      The results are summarized in Table 2 below. Results for all the quality control strains were were within the acceptable range.

Table 2: Quality Control (Eravacycline)

Organism	Conc. (µg/mL)	Reference	Sensititre	
			OptiRead	VIZON
Gram Negative QC Isolates				
E. coli ATCC 25922 Expected Result: 0.03 – 0.12 µg/mL	0.008			
	0.015			
	0.03			
	0.06	72	58	56
	0.12	8	22	24
	0.25			
P. aeruginosa ATCC 27853 Expected Result: 2 – 16 µg/mL	1			
	2	39	72	67
	4	41	8	13
	8			
	16			
	32			
Gram-Positive QC Isolates				
Staphylococcus aureus ATCC 29213 Expected Result: 0.015 – 0.12 µg/mL	0.008			
	0.015		1	
	0.03	21		2
	0.06	56	62	45
	0.12	1	18	34
	0.25			
Enterococcus faecalis ATCC 29212 Expected result: 0.015 – 0.06 µg/mL	0.008			
	0.015	9	4	
	0.03	66	51	30
	0.06	3	16	51
	0.12			

Growth Rate: All 408 non-fastidious Gram negative and 602 non-fastidious Gram positive isolates showed sufficient growth for MIC determination.

Purity Check Plates: Purity checks were performed each day for each clinical, challenge, reproducibility, and QC strain tested.

Inoculum Density Check:
Inoculum density of each quality control, reproducibility, clinical, and challenge isolate was determined each day of testing. The inoculum was prepared to achieve turbidity equivalent to a 0.5 McFarland standard. They were all within acceptable range.

Non-fastidious Gram Negative Organisms: A total of 333 inoculum density checks

were performed for each test and reference plate for clinical isolates, 75 for each for test and reference plate for challenge isolates, 160 for each test and reference panel for QC isolates, and all reproducibility isolates.

Non-fastidious Gram Positive Organisms: A total of 492 inoculum density checks were performed for each test and reference plate for clinical isolates, 108 for each for test and reference plate for challenge isolates, 162 for each test and reference panel for QC isolates, and all reproducibility isolates.

The colony counts obtained for all isolates were within acceptable range.

d. Detection limit:

Not Applicable

e. Analytical specificity:

Not Applicable

f. Assay cut-off:

Not Applicable

2. Comparison studies:

a. Method comparison with predicate device:

The reference plate containing the same antibiotic and dilutions used for the comparison was prepared according to the CLSI recommendation and used as the reference method. During the course of the clinical trial, all Sensititre dried MIC panels were inoculated using the Sensititre Autoinoculator (AIM) and the same panel was read on both the VIZION and the OptiRead in a blinded manner.

A. Non-fastidious Gram Negative Organisms:

Clinical
Clinical testing was conducted at four sites using a total of 333 isolates. Of those, 292 and 41 fresh clinical *Enterobacteriaceae* isolates were from List 1 (*in vitro* and clinical) and List 2 (*in vitro*), respectively. The List 1 included *E. coli* (104), *Klebsiella pneumoniae* (84), *K. oxytoca* (43), *Enterobacter cloacae* (41), and *Citrobacter freundii* (20). The List 2 included *Klebsiella* (*Enterobacter*) *aerogenes* (20) and *Citrobacter koseri* (21).

Challenge
An additional 75 *Enteobacteriaceae* challenge isolates were tested. Of these, 65 and 10 isolates were from List 1 and List 2, respectively. Testing was conducted at one

external site.

The List 1 challenge isolates included the following species: *E. coli* (16), *Klebsiella pneumoniae* (28), *K. oxytoca* (5), *Enterobacter cloacae* (11), and *Citrobacter freundii* (5). Of the 65 List 1 challenge isolates, 43 were non-susceptible to eravacycline by the reference method.

The List 2 challenge isolates included the following species: *Klebsiella* (*Enterobacter*) *aerogenes* (7) and *Citrobacter koseri* (3). Of the 10 List 2 challenge isolates, 4 were non-susceptible to eravacycline by the reference method.

In total, 408 combined (clinical and challenge) *Enteobacteriaceae* isolates were evaluated. Of these, 357 and 51 isolates were from List 1 and List 2, respectively. The EA and CA were above 90% and therefore acceptable. Because of the abscence of intermediate category for Eravacycline, the very major (vmj) discrepancy/error rate was adjusted to 0%. The performance of VIZION and OptiRead of these isolates is shown in Tables 3.1 and 3.2 below.

The growth rate for each plate read in the clinical and challenge studies was 100%.

Table 3.1: Combined (Clinical and Challenge) Performance Summary of *Enterobacteriaceae*- Read by VIZION [*]

Eravacycline	Total	EA N	%EA Total	Tot Eval	EA Eval	%EA Eval	CA N	% CA	#NS	Errors	
										maj	vmj
***Enterobacteriaceae* ≤0.5 (susceptible), --, --**											
Clinical	333	333	100	333	333	100	327	98.2	30	3	3
Challenge	75	75	100	75	75	100	73	97.3	17	0	2
Enterobacteriaceae Total	408	408	100	408	408	100	400	98.0	47	3	5 [a]

[a] Of the 47 non-susceptible isolates, the MIC of the isolates that gave very major (vmj) errors (10.6% vmj rate) were within essential agreement of the reference value; therefore the adjusted vmj rate is 0%

[*] **EA -** Essential Agreement
CA - Category Agreement
NS- Not susceptible
maj – major discrepancies
vmj- very major discrepancies

Evaluable results are those that are on-scale for both the reference panel and the Sensititre panel. Essential agreement (EA) occurs when there is agreement between the MIC result of the reference method and that of Sensititre panel within plus or minus one serial two-fold dilution of the antibiotic. Category agreement occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel result.

Table 3.2: Combined (Clinical and Challenge) Performance Summary of *Enterobacteriaceae*- Read by OptiRead

Eravacycline	Total	EA N	%EA Total	Tot Eval	EA Eval	%EA Eval	CA N	% CA	#NS	Errors	
										maj	vmj
***Enterobacteriaceae* ≤0.5 (susceptible), --, --**											
Clinical	333	333	100	333	333	100	322	96.7	30	7	4
Challenge	75	75	100	75	75	100	72	96.0	17	1	2
Enterobacteriaceae Total	408	408	100	408	408	100	394	96.6	47	8	6 [b]

[b] Of the 47 non-susceptible isolates, the MIC of the isolates that gave vmj errors (12.8% vmj rate) were within essential agreement of the reference value; therefore the adjusted vmj rate is 0%

A comparative evaluation of performance data of the VIZION and OptiRead reading methods showed no notable differences.

Of the 357 List 1 isolates tested, 43 were non-suscepbible. Four and five very major (vmj) discrepancies/errors were observed with the VIZION and OptiRead, respectively. The vmj rate was 9.3% (4/43) for VIZION and 11.6% (5/43) for OptiRead. The vmj errors were from two *Enterobacter cloacae,* one each from *Klebsiella pneumoniae* and *E. coli* using the VIZION, and an additional vmj error from *K. oxytoca* using the OptiRead. All vmj errors were one doubling dilution lower but within essential agreement of the reference method (i.e., reference: 1 µg/mL, Sensititre: 0.5 µg/mL). Due to the lack of intermediate breakpoint for *Enterobacteriaceae* with Eravacycline, the vmj errors that were within EA of the reference can be adjusted to 0% and therefore, acceptable.

Of the 51 List 2 isolates tested, 4 were non-suscepbible. One vmj error was observed with *Citrobacter koseri*. The vmj error rate was 25% (1/4) for both the VIZION and OptiRead reading method. The vmj rate was adjusted to 0% due to the absence of an intermediate category and the MIC value within essential agreement with the reference method.

As a result, the following limitation is included in the device labeling for *Enterobacteriaceae* (non-fastidious Gram negative organisms):

> "There were 47 Eravacycline non-susceptible *Enterobacteriaceae* isolates as determined by the reference method. Although within essential agreement, five and six potential very major (vmj) discrepancies were observed with the VIZION and OptiRead, respectively, due to the lack of intermediate category. When the Sensititre MIC is at the breakpoint of 0.5 µg/mL, testing should be repeated using a reference/alternative testing method prior to reporting results for Eravacycline with *Enterobacter cloacae, E. coli, K. pneumoniae*, or *Citrobacter koseri* with VIZION and *Enterobacter cloacae, E. coli, K. pneumoniae, K. oxytoca,* or *Citrobacter koseri* with OptiRead."

MIC Trends:
MIC trend analysis is provided in Table 3.3 below. All *Enterobacteriaceae* isolates have on-scale MIC values in which a determination could be made of higher or lower

values compared to the reference method. In general, Sensititre results were one-doubling dilution lower than the reference. However, *C. freundii* isolates were notably one-doubling dilution higher as demonstrated in Table 3.4 below when stratified by organism. As a result, the following footnote is included in the performance section of the package insert:

> "Eravacycline MIC values for *Citrobacter freundii* tended to be one doubling dilution higher with the VIZION and the OptiRead as compared to the reference microdilution method."

Table 3.3: MIC Trends for Performance of *Enterobacteriaceae*

Eravacycline	Total	≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher
Enterobacteriaceae						
VIZION	408	0	46	321	41	0
		11.27%		78.68%	10.05%	
		Difference: -1.23%; 95% CI (-5.51, 3.05%)				
OptiRead	408	0	60	298	50	0
		14.71%		73.04%	12.25%	
		Difference: -2.45%; 95% CI (-7.16%, 2.26%)				

Table 3.4: MIC Trends for Performance of *C. freundii*

Eravacycline	Total	≥2 dil. lower	1 dil. lower	Exact	1 dil. higher	≥2 dil. higher
Citrobacter freundii						
VIZION [1]	25	0	0	18	7	0
		0.00%		72.00%	28.00%	
OptiRead [2]	25	0	0	17	8	0
		0.00%		68.00%	32.00%	

[1] Difference between the higher and lower dilutions for VIZION/*C. freundii* is 28.00%; 95% CI (8.88%, 47.58%)

[2] Difference between the higher and lower dilutions for OptiRead/*C. freundii* is: 32.00%; 95% CI (12.09%, 51.59%)

B. Non-Fastidious Gram Positive Organisms

Clinical

Clinical testing was conducted at four sites using a total of 494 of fresh clinical isolates which included 199 MRSA, 201 MSSA, 60 *E. faecalis,* and 34 *E. faecium* isolates.

Challenge

An additional 108 of non-fastidious Gram positive stock organisms were tested at one site which included 50 MRSA, 50 MSSA, 5 *E. faecalis*, and 3 *E. faecium* isolates.

In total, 602 combined (clinical and challenge) isolates were evaluated. The performance of VIZION and the adjusted discrepancy rate of these isolates is shown in Tables 4.1 and 4.2 below, respectively.

Table 4.1: Combined (Clinical and Challenge) Performance Summary of Non-Fastidious Gram Positive- Read by VIZION

Eravacycline	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#NS	Errors	
										maj	vmj
***Staphylococcus aureus* ≤0.06 (Susceptible), --, --**											
Clinical	400	397	99.3	400	397	99.3	365	91.3	34	31	4
Challenge	100	100	100	100	100	100	99	99.0	3	1	0
Combined	500	497	99.4	500	497	99.4	464	92.8	37	32 [a]	4 [b]
***E. faecalis* and *E. faecium* ≤0.06 (Susceptible), --, --**											
E. faecalis											
Clinical	60	57	95.0	60	57	95.0	55	91.7	1	5	0
Challenge	5	5	100	5	5	100	5	100	1	0	0
Combined	65	62	95.4	65	62	95.4	60	92.3	2	5 [c]	0
E. faecium											
Clinical	34	34	100	34	34	100	32	94.1	2	2	0
Challenge	3	3	100	3	3	100	3	100	0	0	0
Combined	37	37	100	37	37	100	35	94.6	2	2 [d]	0
Total	602	596	99.0	602	596	99.0	559	92.9	41	39 [e]	4 [f]

[a] Of the 463 susceptible *S. aureus* isolates, the MIC of 30 of the 32 isolates that gave major (maj) errors (6.9% maj error rate) were within essential agreement of the reference value; therefore the adjusted maj rate is 0.4%

[b] Of the 37 non-susceptible *S. aureus* isolates, the MIC of the 4 isolates that gave vmj errors (10.8% vmj rate) were within essential agreement of the reference value; therefore the adjusted vmj rate is 0%

[c] Of the 63 susceptible *E. faecalis* isolates, the MIC of 3 of the 5 isolates that gave maj errors (7.9% maj error rate) were within essential agreement of the reference value; therefore the adjusted maj rate is 3.2%

[d] Of the 35 susceptible *E. faecium* isolates, the MIC of the 2 isolates that gave maj errors (5.7% maj error rate) were within essential agreement of the reference value; therefore the adjusted maj error rate is 0%

[e] Of the 561 susceptible non-fastidious Gram positive isolates, the MIC of 35 of the 39 isolates that gave maj errors (7.0% maj error rate) were within essential agreement of the reference value, therefore the adjusted major error rate is 0.7%

[f] Of the 41 non-ssuceptible non-fastidious Gram positive isolates, the MIC of the 4 isolates that gave vmj errors (9.8% vmj rate) were within essential agreement of the reference value, therefore the adjusted vmj rate is 0%

Table 4.2: Adjusted Discrepancies (Major and Very Major) Due to the Lack of Intermediate Category for VIZION

Eravacycline	Major Errors			Very Major Errors		
	Susceptible #	#	Rate	Non-Susceptible #	#	Rate
S. aureus						
Before Adjustment	463	32	6.9%	37	4	10.8%
After Adjustment		2	0.4%		0	0%
E. faecalis						
Before Adjustment	63	5	7.9%	2	0	0
After Adjustment		2	3.2%		NA	
E. faecium						
Before Adjustment	35	2	5.7%	2	0	0
After Adjustment		0	0		NA	
Non-fastidious Gram Positive Organisms Combined						
Before Adjustment	561	39	7.0%	41	4	9.8%
After Adjustment		4	0.7%		0	0

The performance of OptiRead and the adjusted discrepancy rate of these isolates is shown in Tables 4.3 and 4.4 below, respectively.

Table 4.3: Combined (Clinical and Challenge) Performance Summary of Non-Fastidious Gram Positive- Read by OptiRead

Eravacycline	Tot	EA N	%EA Total	Total Eval	EA Eval	%EA Eval	CA N	% CA	#NS	Errors	
										maj	vmj
***Staphylococcus aureus* ≤0.06 (Susceptible), --, --**											
Clinical	400	399	99.8	400	399	99.8	378	94.5	34	17	5
Challenge	100	99	99.0	100	99	99.0	95	95.0	3	5	0
Combined	500	498	99.6	500	498	99.6	473	94.6	37	22 [g]	5 [h]
***E. faecalis* and *E. faecium* ≤0.06 (Susceptible), --, --**											
E. faecalis											
Clinical	60	58	96.7	60	58	96.7	59	98.3	1	1	0
Challenge	5	5	100	5	5	100	5	100	1	0	0
Combined	65	63	96.9	65	63	96.9	64	98.5	2	1	0
E. faecium											
Clinical	34	34	100	34	34	100	33	97.1	2	1	0
Challenge	3	3	100	3	3	100	3	100	0	0	0
Combined	37	37	100	37	37	100	36	97.3	2	1	0
Total	602	598	99.3	602	598	99.3	573	95.2	41	24 [i]	5 [j]

[g] Of the 463 susceptible *S. aureus* isolates, the MIC of 21 of the 22 isolates that gave maj errors (4.8% maj error rate) were within essential agreement of the reference value; therefore the adjusted major error rate is 0.2%

[h] Of the 37 non-susceptible *S. aureus* isolates, the MIC of the 5 isolates that gave vmj errors (13.5% vmj rate) were within essential agreement of the reference value; therefore the adjusted vmj rate is 0%

[i] Of the 561 susceptible non-fastidious Gram positive isolates, the MIC of 22 of the 24 isolates that gave maj errors (4.3% maj error rate) were within essential agreement of the reference value, therefore the adjusted major error rate is 0.4%

[j] Of the 41 non-ssuceptible non-fastidious Gram positive isolates, the MIC of the 5 isolates that gave vmj errors (12.2% vmj rate) were within essential agreement of the reference value, therefore the adjusted vmj rate is 0%

Table 4.4: Adjusted Discrepancies (Major and Very Major) Due to the Lack of Intermediate Category for OptiRead Reading Method

Eravacycline	Major Errors			Very Major Errors		
	Susceptible #	#	Rate	Non-Susceptible #	#	Rate
S. aureus						
Before Adjustment	463	22	4.8%	37	5	13.5%
After Adjustment		1	0.2%		0	0%
Non-fastidious Gram Positive Organisms Combined						
Before Adjustment	561	24	4.3%	41	5	12.2%
After Adjustment		2	0.4%		0	0

As shown in Tables 4.1 and 4.3 above, the EA and CA were above 90% (99.0% EA for VIZION and 99.3% EA for OptiRead), and are therefore acceptable.

The CA was 92.9% and 95.9% for VIZION and OptiRead, respectively. There were major (maj) discrepancy/errors and vmj errors with both reading methods. The major (maj) rate was 7.0% (39/561) and vmj rate was 9.8% (4/41) with the VIZION; it was 4.3% (24/561) maj rate and 12.2% (5/41) vmj rate with the OptiRead.

There were a total of 500 *S. aureus* isolates in the studies; maj and vmj errors were observed with both reading methods: maj rate 6.9% (32/463) and vmj rate 10.8% (4/37) with the VIZION; maj rate 4.8% (22/463) and vmj rate 13.5% (5/37) with the OptiRead.

For *E. faecalis* and *E. faecium* isolates, no vmj error was observed with both reading methods. Their maj rates are acceptable by the OptiRead but exceed the acceptance criteria at 7.9% (5/63) for *E. faecalis* and 5.7% (2/35) for *E. faecium* by VIZION.

Due to the lack of intermediate breakpoints for *S. aureus, E. faecalis,* and *E. faecium* with Eravacycline, errors (maj and vmj) that were within EA of the reference can be adjusted. As a result, the following limitation is included in the device labeling for non-fastidious gram positive organisms (*S. aureus, E. faecalis,* and *E. faecium*):

> "There were 561 Eravacycline susceptible gram positive (non-fastidious) isolates as determined by the reference method. Although within essential agreement, 39 and 24 potential major (maj) discrepancies were observed with the VIZION and OptiRead, respectively, due to the lack of an intermediate category. When the Sensititre MIC is at 0.12 µg/mL, the non-susceptible breakpoint, testing should be repeated using a reference/alternative testing method prior to reporting results for Eravacycline with *S. aureus, E. faecalis*, and *E. faecium* for the VIZION reading method and *S. aureus* with the OptiRead reading method."

> "There were 41 Eravacycline non-susceptible gram positive (non-fastidious) isolates as determined by the reference method. Although within essential agreement, four and five potential very major (vmj) discrepancies were observed with the VIZION and OptiRead, respectively, due to the lack of intermediate category. When the Sensititre MIC is at the breakpoint of 0.06 µg/mL, testing

should be repeated using a reference/alternative testing method prior to reporting results for Eravacycline with *Staphylococcus aureus* with VIZION and with OptiRead."

MIC Trends

All non-fastidious Gram positive isolates have on-scale MIC values in which a determination could be made of higher or lower values compared to the reference method. As demonstrated in Table 5 below, there was a difference in results trending higher when compared to the reference method. It was consistently one doubling dilution higher for both VIZION and OptiRead methods. For VIZION, it was 69.60% (419/602) one-doubling dilution higher while those equal to the reference (exact) was only 27.74% (167/602). It was 58.97% one dilution higher and 37.54% exact for OptiRead.

Table 5: MIC Trends for Performance of Non-Fastidious Gram Positive (*S. aureus, E. faecalis,* and *E. faecium*)

Eravacycline	Total	2 dil. lower	1 dil. lower	Exact	1 dil. higher	2 dil. higher
VIZION	602	0	10	167	419	6
		0	1.66%	27.74%	**69.60%**	1.00%
		1.66% [1]			70.60% [1]	
OptiRead	602	0	17	226	355	4
		0	2.82%	37.54%	**58.97%**	0.66%
		2.82% [2]			359 (59.63%) [2]	

[1] Difference between the higher and lower dilutions for VIZION is 68.94%; 95% CI (64.93%, 72.52%)
[2] Difference between the higher and lower dilutions for OptiRead is 56.81%; 95% CI (52.51%, 60.80%)

It was observed that the susceptible Gram positive isolates were clustered around the Eravacycline breakpoint. There were 147 isolates (128 *S. aureus* and 19 *Enterococcus* spp.) at the breakpoint of 0.06 µg/mL by the reference method. The maj rate was 7.0% (39/561) and 4.3% (24/561) for VIZION and OptiRead, respectively. The Sensititre trends of one dilution higher raise concerns of potential maj discrepancies for Eravacycline. As a result, the following footnotes to the performance table was included:

"Eravacycline MIC values for *Staphylococcus aureus, Enterococcus faecalis*, and *Enterococcus faecium* tended to be one doubling-dilution higher with the VIZION as compared to the reference microdilution method**.** When the Sensititre MIC is at the non-susceptible breakpoint of 0.12 µg/mL, testing should be repeated using a reference/alternative testing method prior to reporting results for Eravacycline with *S. aureus, E. faecalis,* and *E. faecium."*

"Eravacycline MIC values for *Staphylococcus aureus, Enterococcus faecalis*, and *Enterococcus faecium* tended to be one doubling-dilution higher with the OptiRead as compared to the reference microdilution method**.** When the Sensititre MIC is at the non-susceptible breakpoint of 0.12 µg/mL, testing should be repeated using a reference/alternative testing method prior to reporting results for Eravacycline with *S. aureus."*

Gram positive isolates were initially evaluated using a dilution range of 0.001– 16 µg/mL as presented in the 510(k) submission; however, during the review, the sponsor requested that the same dilution range be considered for Gram positive as the dilution range used for Gram negative organisms (i.e., 0.008 – 16 µg/mL). Given that all results were on-scale for Gram positive organisms using the truncated range, the data demonstrated identical performance for all parameters compared to the original analysis using the 0.001– 16 µg/mL range. Therefore, the data supports the 0.008– 16 µg/mL dilution range claim for Gram positive organisms.

In addition, the following sub-section is added to the Reading Test Results section of the Instuction For Use:

> **"b. Difficult Microdilution Endpoints**
> Trailing growth may occur with some organism/antimicrobic combinations. With some combinations, the MIC values may be higher by VIZION or OptiRead when compared to the reference method. This can be observed with certain antimicrobial agents like tetracyclines (e.g., Eravacycline with *Staphylococcus aureus*, *Enterococcus faecalis*, or *Enterococcus faecium*)."

Resistance Markers in Challenge Isolates
Resistance markers for indicated *Enterobacteriaceae* were provided in the submission. They consisted mostly of βeta-lactamses including ESBL (CTX-M, TEM, SHV), carbapenemases (KPC, NDM, OXA, VIM, IMP), cAmpC, pAmpC (CMY-2, ACT/MIR), OXY, and outer membrane porin (OMPC, OMPK-36).

Gram positive and Gram negative strains expressing tetracycline-specfic resistance mechanisms(s) such as efflux mediated by tet(A), tet(B), and tet(K) and ribosomal protection encoded by tet(M) and tet(Q) were not available for evaluation. As a results, the information regarding these resistance mechanisms is included in the limitation sections of the device labeling:

> "***Gram Negative Organisms***
> Resistance mechanism characterization was not available for all organisms at the time comparative testing, and therefore the performance of the Sensititre Eravacycline is unknown for *Enterobacteriaceae* with efflux mediated by tet(A), and tet(B).
>
> ***Gram Positive Organisms***
> Resistance mechanism characterization was not available for all organisms at the time comparative testing, and therefore the performance of the Sensititre Eravacycline is unknown for non-fastidious gram-positive (*Staphylococcus aureus, Enterococcus faecalis,* and *Enterococcus faecium*) isolates with efflux mediated by tet(K) and ribosomal protection as encoded by tet(M)."

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The FDA susceptibility interpretive criteria for Eravacycline are listed in Table 6.

Table 6: Interpretative Criteria for Eravacycline (µg/mL)

	Susceptible (S)	**Intermediate (I)**	**Resistant (R)**
*Enterobacteriaceae**	≤0.5	--	--
Staphylococcus aureus	≤0.06	--	--
Enterococcus faecalis and *Enterococcus faecium*	≤0.06	--	--

* Clinical efficacy was shown for *Citrobacter freundii, Enterobacter cloacae, Escherichia coli, Klebsiella oxytoca,* and *Klebsiella pneumoniae*.

N. Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.