



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

I Background Information:

A 510(k) Number

K250575

B Applicant

Thermo Fisher Scientific

C Proprietary and Established Names

The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Aztreonam/avibactam in the dilution range of 0.008/4-64/4 µg/mL

D Regulatory Information

| Product Code(s) | Classification | Regulation Section | Panel |
|-----------------|----------------|--|-------------------|
| JWY | Class II | 21 CFR 866.1640 - Antimicrobial Susceptibility Test Powder | MI - Microbiology |
| LRG | Class II | 21 CFR 866.1640 - Antimicrobial susceptibility test powder | MI - Microbiology |
| LTT | Class II | 21 CFR 866.1640 - Antimicrobial susceptibility test powder | MI - Microbiology |

II Submission/Device Overview:

A Purpose for Submission:

To obtain substantial equivalence determination for The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Aztreonam/avibactam in the dilution range 0.008/4–64/4 µg/mL.

B Measurand:

Aztreonam/avibactam in the dilution range 0.008/4 to 64/4 µg/mL

C Type of Test:

Quantitative antimicrobial susceptibility test (AST) growth-based detection

III Intended Use/Indications for Use:

A 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 *Acinetobacter* species, Enterobacterales, *Pseudomonas aeruginosa*, and other non-Enterobacterales and of non-fastidious Gram positive isolates, comprising of *Staphylococcus* spp., *Enterococcus* spp., and beta-haemolytic Streptococci other than *S. pneumoniae*.

B 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 aztreonam/avibactam in the dilution range of 0.008/4-64/4 µg/mL for testing non-fastidious gram-negative isolates on The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System. Testing is indicated for Enterobacterales, as recognized by the FDA Susceptibility Test Interpretive Criteria (STIC) webpage.

The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Aztreonam/avibactam in the dilution range of 0.008/4-64/4 µg/mL has demonstrated acceptable performance with the following organisms:

Enterobacterales (*Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter cloacae* complex, *Escherichia coli*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Morganella morganii*, *Proteus mirabilis*, *Proteus vulgaris*, *Providencia rettgeri*, *Providencia stuartii*, *Serratia marcescens*)

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

The following limitation was applied to aztreonam/avibactam testing in the appropriate sections of the device labeling that reference other drugs:

Studies of the following drugs were performed with the AIM Autoinoculator and read using the ARIS HiQ/OptiRead and Vizion. The use of an alternative inoculation system or alternative read methods has not been evaluated.

Due to the insufficient number of resistant *C. freundii*, *C. koseri*, *E. cloacae* complex, *K. aerogenes*, *K. oxytoca*, *M. morganii*, *P. mirabilis*, *P. rettgeri*, *P. stuartii*, *P. vulgaris*, and *S. marcescens* isolates evaluated, the following limitation was applied to aztreonam/avibactam testing in the appropriate section of the device labeling that references other drugs:

The ability of the Sensititre system to detect resistance or non-susceptibility to antimicrobics as shown below is unknown because an insufficient number of

resistant or non-susceptible strains were available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.

D Special Instrument Requirements:

Sensititre AIM for device inoculation
Sensititre Vizion digital viewing device
Sensititre ARIS HiQ/OptiRead automated plate reader

IV Device/System Characteristics:

A Device Description:

The Sensititre 18-24 hour MIC or Breakpoint Susceptibility Plate System is an antimicrobial susceptibility test. Each plate is dosed with dried, stabilized antimicrobial agents at appropriate dilutions. It is a micro-version of the classic broth dilution method 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.

B Principle of Operation:

The Sensititre 18-24 hour MIC Susceptibility plates are multi-well plastic microtiter plates that contain doubled dilutions of antibacterial agents. Each plate includes antimicrobial agents at appropriate dilutions. Results can be read using the digital viewing device (Vizion) or by use of an automated plate reader (ARIS HiQ/OptiRead).

The Sensititre Vizion digital viewing device allows the panel image to be displayed on a touch screen directly from a video camera and allows the user to visually determine 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 non-fluorescent 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 bound non-fluorescent substrate cleaves the bond releasing fluorescence. The amount of fluorescence detected is directly related to the activity of bacterial growth. The MIC is determined by observing the lowest dilution of antimicrobial agent that inhibits growth of the organism. The non-fluorescent (fluorogenic) 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.

Sensititre 18-24 hour MIC plates can either be read automatically on an ARIS HiQ/OptiRead using fluorescence or by visual reading of growth on the Vizion digital viewing device.

V Substantial Equivalence Information:

A Predicate Device Name(s):

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

B Predicate 510(k) Number(s):

K243169

C Comparison with Predicate(s):

| Device & Predicate Device(s): | Device <u>K250575</u> | <u>Predicate</u> <u>K243169</u> |
|---|--|---|
| Device Trade Name | The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Aztreonam/avibactam in the dilution range of 0.008/4-64/4 µg/mL | The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Ceftobiprole in the dilution range of 0.008-16 µg/mL |
| General Device Characteristic Similarities | | |
| Intended Use | The Sensititre 18-24 Hour MIC or Breakpoint Susceptibility System is an <i>in vitro</i> diagnostic product for clinical susceptibility testing of non-fastidious bacterial isolates. | Same |
| Test Panel | Each 96 well plate is precision dosed with selected antimicrobial agents and substrate for the fluorescent reads, then dried. The bacterial suspension in the appropriate broth is used to rehydrate the plate. | Same |
| Incubation | 18–24 hours | |
| Read Method | Results can be read using fluorescence with the ARIS HiQ/OptiRead or by visual reading of growth with the Vizion. | |
| General Device Characteristic Differences | | |
| Antibiotic and Dilution Range | Aztreonam/avibactam 0.008/4-64/6 µg/mL | Ceftobiprole 0.008-16 µg/mL |
| Test Organism(s) | <i>Enterobacteriales (Citrobacter freundii, Citrobacter koseri, Enterobacter cloacae complex, Escherichia coli, Klebsiella aerogenes, Klebsiella oxytoca, Klebsiella pneumoniae, Morganella morganii, Proteus mirabilis, Proteus vulgaris, Providencia rettgeri,</i> | <i>Staphylococcus aureus</i> (including methicillin-resistant isolates) |

| | | |
|--|--|--|
| | <i>Providencia stuartii</i> , <i>Serratia marcescens</i>) | |
|--|--|--|

VI Standards/Guidance Documents Referenced:

CLSI M07, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard - Eleventh Edition", (January 2018)

CLSI M100, "Performance Standards for Antimicrobial Susceptibility Testing; 34th Edition", (March 2024)

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

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

A reproducibility study of The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Aztreonam/avibactam was performed at four sites using a panel of eight (8) gram-negative isolates from species indicated for use with the device (2 *Escherichia coli*, 2 *Klebsiella pneumoniae*, 2 *Klebsiella aerogenes*, 1 *Enterobacter cloacae*, and 1 *Citrobacter freundii*). Aztreonam/avibactam MIC values were on-scale for all these isolates.

In addition, one *Proteus mirabilis* isolate with an off-scale mode was tested. Further, one *Pseudomonas aeruginosa* isolate that does not have FDA-recognized STIC breakpoints for aztreonam/avibactam and is not intended for use with the device was tested. To complete evaluation with on-scale MIC values, a supplementary reproducibility study was performed at one site using a panel of two isolates from species indicated for testing with the device (1 *Klebsiella aerogenes* and 1 *Proteus mirabilis*).

All on-scale isolates with STIC-recognized breakpoints were tested in triplicate over three days for a total of 306 data points with each read method (i.e., automatically with the ARIS HiQ/OptiRead and visually with the Vizion). The Sensititre AIM Autoinoculator was used for Sensititre plate inoculation. The mode MIC value was determined, and the reproducibility was calculated based on MIC values falling within ± 1 doubling dilution of the mode MIC value. The combined original and supplemental reproducibility studies for both the ARIS HiQ/OptiRead and Vizion read methods demonstrated acceptable performance of $\geq 95\%$.

2. Linearity:

Not applicable.

3. Analytical Specificity/Interference:

Not applicable.

4. Assay Reportable Range:

Not applicable.

5. Traceability, Stability, Expected Values (Controls, Calibrators, or Methods):

The CLSI-recommended quality control (QC) strain *K. pneumoniae* ATCC 700603 and three other CLSI QC strains, *E. coli* ATCC 25922, *E. coli* ATCC 35218, and *P. aeruginosa* ATCC 27853, were tested at four sites. The QC strains were tested a minimum of 20 times per site and read automatically with the ARIS HiQ/OptiRead and visually with the Vizion. The QC strains were also tested with the reference method. The results demonstrate that The Sensititre 18-24 hour MIC Susceptibility System with Aztreonam/avibactam produced quality control results within the recommended range >95% of the time (**Table 1**).

Table 1. Quality Control Results for *K. pneumoniae*, *E. coli*, and *P. aeruginosa* with Aztreonam/avibactam with the Reference Method, ARIS HiQ/OptiRead, and Vizion

| QC Organism | Expected Range (µg/mL) | Concentration (µg/mL) | Reference | ARIS HiQ/OptiRead | Vizion |
|---|-------------------------|-----------------------|-----------|-------------------|--------|
| <i>Klebsiella pneumoniae</i> ATCC 700603 | 0.06/4-0.5/4 µg/mL | ≤0.03/4 | - | - | - |
| | | 0.06/4 | 15 | - | - |
| | | 0.12/4 | 27 | 93 | 91 |
| | | 0.25/4 | 50 | 6 | 8 |
| | | 0.5/4 | 2 | - | - |
| | ≥1/4 | - | 1 | 1 | |
| <i>Escherichia coli</i> ATCC 25922 | 0.03/4-0.12/4 µg/mL | ≤0.0015/4 | - | - | - |
| | | 0.03/4 | 1 | 2 | 2 |
| | | 0.06/4 | 34 | 93 | 91 |
| | | 0.12/4 | 54 | 3 | 7 |
| | | ≥0.25/4 | 5 | 1 | - |
| <i>Escherichia coli</i> ATCC 35218 | 0.015/4-0.06/4 µg/mL | ≤0.008/4 | - | - | 1 |
| | | 0.015/4 | 18 | 70 | 55 |
| | | 0.03/4 | 69 | 24 | 40 |
| | | 0.06/4 | 6 | - | - |
| | | ≥0.12/4 | - | 1 | - |
| <i>Pseudomonas aeruginosa</i> ATCC 27853 | 2/4-8/4 µg/mL | ≤1/4 | 2 | - | 1 |
| | | 2/4 | 9 | 78 | 71 |
| | | 4/4 | 76 | 22 | 24 |
| | | 8/4 | 6 | - | 4 |
| | | ≥16/4 | 1 | - | - |

Inoculum Density: Inoculum density checks were performed for all QC, reproducibility, challenge, and clinical isolates tested. Only results from cultures with appropriate inoculum densities were reported.

Purity Checks: Purity checks were performed for all QC, reproducibility, challenge, and clinical isolates tested. Only results from pure cultures were reported.

Growth Failure: There were no growth failures for Enterobacterales.

ARIS HiQ/OptiRead Invalid (No fluorescence): There were no invalids for Enterobacterales that did not produce adequate fluorescence by the ARIS HiQ/OptiRead.

6. Detection Limit:

Not applicable.

7. Assay Cut-Off:

Not applicable.

B Comparison Studies:

1. Method Comparison with Predicate Device:

Testing of The Sensititre 18-24 hour MIC or Breakpoint Susceptibility System with Aztreonam/avibactam was performed at three external sites and one internal site. Results were compared to those obtained with the CLSI broth microdilution reference method. Sensititre panels were inoculated using only the AIM Autoinoculator and results were read automatically by the ARIS HiQ/OptiRead and visually by the Vizion. Reference panels were inoculated according to recommendations in the M07 CLSI document and results were read manually using a mirrored reader.

No inoculation system other than the AIM Autoinoculator and no read method other than ARIS HiQ/OptiRead and Vizion was used in the comparative study. To address the inoculation method and read method limitation, the following limitation was applied to aztreonam/avibactam testing in the appropriate sections of the device labeling that reference other drugs:

Studies of the following drugs were performed with the AIM Autoinoculator and read using the ARIS HiQ/OptiRead and Vizion. The use of an alternative inoculation system or alternative read methods has not been evaluated.

The testing conditions for the reference method consisted of the following:

- Media: per CLSI M07 guidelines for Enterobacterales
- Inoculum: Inoculated per CLSI M07 guidelines
- Incubation: 34-36° C in a non-CO₂ incubator for 16-20 hours

Inoculation and incubation procedure for Enterobacterales (excluding *Proteus* spp., *Providencia* spp., and *Morganella* spp.)

- Media: cation-adjusted Mueller Hinton broth with TES buffer (CAMHBT)
- Inoculum: A suspension approximating a 0.5 McFarland standard was prepared in 5 mL sterile water. Ten (10) µL of the standardized suspension was transferred to 11 mL of

CAMHBT. Susceptibility plates were inoculated with 50 µL of the final organism suspension using the Sensititre AIM Autoinoculator.

- Incubation: 34-36° C in a non-CO₂ incubator for 18-24 hours

Inoculation and incubation procedure for *Proteus* spp., *Providencia* spp., and *Morganella* spp.

- Media: cation-adjusted Mueller Hinton broth with TES buffer (CAMHBT)
- Inoculum: A suspension approximating a 0.5 McFarland standard was prepared in 5 mL sterile water. One (1.0) µL of the standardized suspension was transferred to 11 mL of CAMHBT. Susceptibility plates were inoculated with 50 µL of the final organism suspension using the Sensititre AIM Autoinoculator.
- Incubation: 34-36° C in a non-CO₂ incubator for 18-24 hours

ARIS HiQ/OptiRead:

A total of 518 gram-negative clinical isolates comprised of Enterobacteriales (20 *C. freundii*, 20 *C. koseri*, 60 *E. cloacae* complex, 80 *E. coli*, 40 *K. aerogenes*, 20 *K. oxytoca*, 80 *K. pneumoniae*, 80 *M. morgani*, 40 *P. mirabilis*, 19 *P. rettgeri*, 19 *P. stuartii*, 20 *P. vulgaris*, and 20 *S. marcescens* isolates), as well as 179 challenge isolates comprised of Enterobacteriales (9 *C. freundii*, 9 *C. koseri*, 19 *E. cloacae* complex, 40 *E. coli*, 13 *K. aerogenes*, 7 *K. oxytoca*, 35 *K. pneumoniae*, 14 *M. morgani*, 11 *P. mirabilis*, 5 *P. rettgeri*, 5 *P. stuartii*, 5 *P. vulgaris*, and 7 *S. marcescens* isolates) were evaluated and the results are provided in **Table 2**.

For Enterobacteriales read using the ARIS HiQ/OptiRead, the combined clinical and challenge isolates (697 isolates) were acceptable at 94.7% and 98.7% for EA and CA, respectively. There were 5 minor errors, 3 major errors (3/680 = 0.4%), and 1 very major error (1/14 = 7.1%). When evaluating by individual species, the very major error was due to a *S. marcescens* isolate (1/1 = 100%). Due to the lack of resistant *S. marcescens* isolates evaluated, the very major error is considered random, and the following performance footnote was included in the device labeling:

The 1 very major error observed was considered a random error due to the limited number of resistant isolates tested for S. marcescens.

When evaluating by individual species, the EA for *K. aerogenes* was 86.8% (46/53) when read with the ARIS HiQ/OptiRead and is not acceptable. A supplemental study was performed to address the unacceptable EA and is described below.

Table 2. Aztreonam/avibactam Performance of Enterobacteriales read by ARIS HiQ/OptiRead

| | Tot | EA No. | EA % | Eval Tot | Eval EA No. | Eval EA % | CA Tot | CA % | No. R | No. S | min | maj | vmj |
|--|-----|--------|------|----------|-------------|-----------|--------|------|-------|-------|-----|-----|-----|
| Enterobacteriales [$\leq 4/4$ (S), $8/4$ (I), $\geq 16/4$ (R)] | | | | | | | | | | | | | |
| Clinical | 518 | 496 | 95.8 | 382 | 360 | 94.2 | 514 | 99.2 | 2 | 516 | 0 | 3 | 1 |
| Challenge | 179 | 164 | 91.6 | 154 | 139 | 90.3 | 174 | 97.2 | 12 | 164 | 5 | 0 | 0 |
| Total | 697 | 660 | 94.7 | 536 | 499 | 93.1 | 688 | 98.7 | 14 | 680 | 5 | 3 | 1 |

EA – Essential Agreement
 CA – Category Agreement
 S – Susceptible
 R – Resistant

EVAl – Evaluable MICs
 min – Minor Discrepancies
 maj – Major Discrepancies
 vmj – Very Major Discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the Sensititre panel or those in which an off-scale result is at least two doubling dilutions from the on-scale result. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

Vizion:

A total of 518 gram-negative clinical isolates comprised of Enterobacteriales (20 *C. freundii*, 20 *C. koseri*, 60 *E. cloacae* complex, 80 *E. coli*, 40 *K. aerogenes*, 20 *K. oxytoca*, 80 *K. pneumoniae*, 80 *M. morgani*, 40 *P. mirabilis*, 19 *P. rettgeri*, 19 *P. stuartii*, 20 *P. vulgaris*, and 20 *S. marcescens* isolates), as well as 179 challenge isolates comprised of Enterobacteriales (9 *C. freundii*, 9 *C. koseri*, 19 *E. cloacae* complex, 40 *E. coli*, 13 *K. aerogenes*, 7 *K. oxytoca*, 35 *K. pneumoniae*, 14 *M. morgani*, 11 *P. mirabilis*, 5 *P. rettgeri*, 5 *P. stuartii*, 5 *P. vulgaris*, and 7 *S. marcescens* isolates) were evaluated and the results are provided in **Table 3**.

For Enterobacteriales read using the Vizion the combined clinical and challenge isolates (697 isolates) were acceptable at 95.8% and 99.6% for EA and CA, respectively. There were 3 minor errors, no major errors, and no very major errors.

When evaluating by individual species, the EA for *K. aerogenes* was 88.7% (47/53) when read with the Vizion and is not acceptable. A supplemental study was performed to address the unacceptable EA and is described below.

Table 3. Aztreonam/avibactam Performance of Enterobacteriales read by Vizion

| | Tot | EA No. | EA % | Eval Tot | Eval EA No. | Eval EA % | CA Tot | CA % | No. R | No. S | min | maj | vmj |
|--|-----|--------|------|----------|-------------|-----------|--------|------|-------|-------|-----|-----|-----|
| Enterobacteriales ≤ 4/4 (S), 8/4 (I), ≥16/4 (R) | | | | | | | | | | | | | |
| Clinical | 518 | 502 | 96.9 | 383 | 367 | 95.8 | 518 | 100 | 2 | 516 | 0 | 0 | 0 |
| Challenge | 179 | 166 | 92.7 | 154 | 141 | 91.6 | 176 | 98.3 | 12 | 164 | 3 | 0 | 0 |
| Total | 697 | 668 | 95.8 | 537 | 508 | 94.6 | 694 | 99.6 | 14 | 680 | 3 | 0 | 0 |

EA – Essential Agreement
 CA – Category Agreement
 S – Susceptible
 R – Resistant

EVAl – Evaluable MICs
 min – Minor Discrepancies
 maj – Major Discrepancies
 vmj – Very Major Discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the Sensititre panel or those in which an off-scale result is at least two doubling dilutions from the on-scale result. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

Supplemental Testing:

The EA for *K. aerogenes* read by ARIS HiQ/OptiRead and Vizion in the original study was unacceptable. To address this, additional *K. aerogenes* challenges isolates (30) were tested and read by the ARIS HiQ/OptiRead and Vizion in a supplemental study performed at one internal site. The results from the supplemental *K. aerogenes* testing were acceptable at 100% EA and 100% CA with no errors. The original and supplemental data was combined, and the EA for 83

K. aerogenes isolates was acceptable at 91.6% and 92.8% when read by the ARIS HiQ/OptiRead and Vizion, respectively.

The Enterobacterales original and clinical challenge data were combined with the supplemental testing. The final results demonstrated an acceptable EA of 94.9% with the ARIS HiQ/OptiRead and 96.0% with the Vizion (Table 4).

Table 4. Combined (Original and Supplemental) Aztreonam/avibactam Performance of Enterobacterales Read by ARIS HiQ/OptiRead and Vizion

| | Tot | EA No. | EA % | Eval Tot | Eval EA No. | Eval EA % | CA Tot | CA % | No. R | No. S | min | maj | vmj |
|---|-----|--------|------|----------|-------------|-----------|--------|------|-------|-------|-----|-----|-----|
| Enterobacterales [$\leq 4/4$ (S), $8/4$ (I), $\geq 16/4$ (R)] | | | | | | | | | | | | | |
| ARIS HiQ/OptiRead | | | | | | | | | | | | | |
| Clinical | 518 | 496 | 95.8 | 382 | 360 | 94.2 | 514 | 99.2 | 2 | 516 | 0 | 3 | 1 |
| Challenge | 179 | 164 | 91.6 | 154 | 139 | 90.3 | 174 | 97.2 | 12 | 164 | 5 | 0 | 0 |
| Supplemental* | 30 | 30 | 100 | 30 | 30 | 100 | 30 | 100 | 0 | 30 | 0 | 0 | 0 |
| Total | 727 | 690 | 94.9 | 566 | 529 | 93.5 | 718 | 98.8 | 14 | 710 | 5 | 3 | 1 |
| Vizion | | | | | | | | | | | | | |
| Clinical | 518 | 502 | 96.9 | 383 | 367 | 95.8 | 518 | 100 | 2 | 516 | 0 | 0 | 0 |
| Challenge | 179 | 166 | 92.7 | 154 | 141 | 91.6 | 176 | 98.3 | 12 | 164 | 3 | 0 | 0 |
| Supplemental* | 30 | 30 | 100 | 30 | 30 | 100 | 30 | 100 | 0 | 30 | 0 | 0 | 0 |
| Total | 727 | 698 | 96.0 | 567 | 538 | 94.9 | 724 | 99.6 | 14 | 710 | 3 | 0 | 0 |

*Supplemental testing performed with *K. aerogenes* isolates

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 R – Resistant

EVAl – Evaluable MICs
 min – Minor Discrepancies
 maj – Major Discrepancies
 vmj – Very Major Discrepancies

Essential agreement (EA) occurs when the result of the reference method and that of the Sensititre panel are within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the reference method and the Sensititre panel or those in which an off-scale result is at least two doubling dilutions from the on-scale result. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the Sensititre panel.

Due to the insufficient number of resistant *C. freundii*, *C. koseri*, *E. cloacae* complex, *K. aerogenes*, *K. oxytoca*, *M. morgani*, *P. mirabilis*, *P. rettgeri*, *P. stuartii*, *P. vulgaris*, and *S. marcescens* isolates evaluated, the following limitation was applied to aztreonam/avibactam testing in the appropriate section of the device labeling that references other drugs:

The ability of the Sensititre system to detect resistance or non-susceptibility to antimicrobics as shown below is unknown because an insufficient number of resistant or non-susceptible strains were available at the time of comparative testing. If such a strain is observed, it should be submitted to a reference laboratory.

MIC Trending

A trending analysis was conducted using the combined data (clinical and challenge) obtained for both the ARIS HiQ/OptiRead and the Vizion for Enterobacterales. This trending calculation takes into account MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method irrespective of whether the device MIC values are on-scale or not.

Species for which the difference between the percentage of isolates with higher vs. lower readings was > 30% and for which the confidence interval was determined to be statistically significant were considered to show evidence of trending. Trending that shows higher or lower MIC values compared to the reference is addressed in the labeling.

Evaluation of results for the species within Enterobacterales with aztreonam/avibactam using the ARIS HiQ/OptiRead and Vizion are summarized in **Table 5**. A trend toward higher MIC values was observed for *K. oxytoca* using the ARIS/HiQ/OptiRead when compared to the CLSI broth microdilution reference method. A trend toward lower MIC values was observed for *E. coli*, *P. rettgeri*, and *P. vulgaris* using the ARIS/HiQ/OptiRead when compared to the CLSI broth microdilution reference method. A trend toward higher MIC values was observed for *K. oxytoca* using the Vizion when compared to the CLSI broth microdilution reference method. A trend toward lower MIC values was observed for *E. coli* and *P. rettgeri* using the Vizion when compared to the CLSI broth microdilution reference method.

To address the MIC trending, the sponsor includes the following footnotes in the performance table:

For ARIS HiQ/OptiRead:

Aztreonam/avibactam MIC values tended to be in exact agreement or at least one doubling dilution higher when testing K. oxytoca with the ARIS HiQ/OptiRead compared to the CLSI reference broth microdilution method.

Aztreonam/avibactam MIC values tended to be in exact agreement or at least one doubling dilution lower when testing E. coli, P. rettgeri, and P. vulgaris with the ARIS HiQ/OptiRead compared to the CLSI reference broth microdilution method.

For Vizion:

Aztreonam/avibactam MIC values tended to be in exact agreement or at least one doubling dilution higher when testing K. oxytoca with the Vizion compared to the CLSI reference broth microdilution method.

Aztreonam/avibactam MIC values tended to be in exact agreement or at least one doubling dilution higher when testing E. coli and P. rettgeri with the Vizion compared to the CLSI reference broth microdilution method.

Table 5. Aztreonam/avibactam Trending Analysis for Enterobacterales with ARIS HiQ/OptiRead and Vizion

| Read Method | Organism | Total Evaluable for Trending | ≥ 1 Dilution lower No. (%) | Exact No. (%) | ≥ 1 Dilution Higher No. (%) | Percent Difference (95% CI) | Trending Noted |
|-------------|---------------------------|------------------------------|----------------------------|---------------|-----------------------------|-----------------------------|----------------|
| | <i>C. freundii</i> | 29 | 9, (31.0) | 13 | 7 (24.1) | -7% (-29% to 16%) | No |
| | <i>C. koseri</i> | 29 | 4, (13.8) | 15 | 10, (34.5) | 21% (-2% to 41%) | No |
| | <i>E. cloacae</i> complex | 78 | 28, (35.9) | 31 | 19, (24.4) | -12% (-25% to 3%) | No |

| Read Method | Organism | Total Evaluable for Trending | ≥ 1 Dilution lower No. (%) | Exact No. (%) | ≥ 1 Dilution Higher No. (%) | Percent Difference (95% CI) | Trending Noted |
|----------------------|---------------------------|------------------------------|----------------------------|---------------|-----------------------------|-----------------------------|----------------|
| ARIS HiQ/OptiRead | <i>E. coli</i> | 110 | 53, (48.2) | 51 | 6, (5.5) | -43% (-52% to -32%) | Yes, low |
| | <i>K. aerogenes</i> | 82 | 26, (31.7) | 24 | 32, (39.0) | 7% (-7% to 21%) | No |
| | <i>K. oxytoca</i> | 27 | 5, (18.5) | 9 | 13, (48.2) | 30% (4% to 50%) | Yes, high |
| | <i>K. pneumoniae</i> | 114 | 33, (29.0) | 31 | 50, (43.9) | 15% (2% to 27%) | No |
| | <i>M. morgani</i> | 81 | 18, (22.2) | 43 | 20, (24.7) | 2% (-11 to 15%) | No |
| | <i>P. mirabilis</i> | 4 | 2, (50.0) | 1 | 1, (25.0) | -25% (-66% to 32%) | No |
| | <i>P. rettgeri</i> | 7 | 4, (57.1) | 3 | 0, (0.0) | -57% (-84% to 9%) | Yes, low |
| | <i>P. stuartii</i> | 13 | 4, (30.8) | 4 | 5, (38.5) | 8% (-26% to 39%) | No |
| | <i>P. vulgaris</i> | 6 | 4, (66.7) | 1 | 1, (16.7) | -50% (-77% to 4%) | Yes, low |
| | <i>S. marcescens</i> | 27 | 6, (22.2) | 17 | 4, (14.8) | -7%, (-28% to 14%) | No |
| Vizion | <i>C. freundii</i> | 29 | 8, (27.6) | 12 | 9, (31.0) | 3% (-19% to 26%) | No |
| | <i>C. koseri</i> | 27 | 4, (14.8) | 15 | 8, (29.6) | 15% (-8% to 36%) | No |
| | <i>E. cloacae complex</i> | 77 | 29, (37.7) | 31 | 17, (22.1) | -16% (-29% to -1%) | No |
| | <i>E. coli</i> | 111 | 45, (40.5) | 57 | 9, (8.1) | -32% (-42% to -22%) | Yes, low |
| | <i>K. aerogenes</i> | 82 | 25, (30.5) | 24 | 33, (40.2) | -10% (-5% to 24%) | No |
| | <i>K. oxytoca</i> | 27 | 5, (18.5) | 9 | 13, (48.2) | 30% (4% to 50%) | Yes, high |
| | <i>K. pneumoniae</i> | 113 | 33, (29.2) | 28 | 52, (46.0) | 17% (4% to 29%) | No |
| | <i>M. morgani</i> | 84 | 15, (17.9) | 45 | 24, (28.6) | 11% (-2% to 23%) | No |
| | <i>P. mirabilis</i> | 4 | 2, (50.0) | 1 | 1, (25.0) | -25% (-66% to 32%) | No |
| | <i>P. rettgeri</i> | 7 | 4, (57.1) | 3 | 0, (0.0) | -57% (-84% to 9%) | Yes, low |
| | <i>P. stuartii</i> | 11 | 4, (36.4) | 5 | 2, (18.2) | -18% (-49% to 18%) | No |
| | <i>P. vulgaris</i> | 6 | 2, (33.3) | 3 | 1, (16.7) | -17% (-56% to 30%) | No |
| <i>S. marcescens</i> | 26 | 6, (23.1) | 14 | 6, (23.1) | 0%(-22% to 22%) | No | |

Testing/Reporting MICs for Species Not Listed in the Indications for Use

For this review, the interpretive criteria are applied to the organisms/organism groups according to the FDA STIC website. As required under 511A(2)(2)(B) of the Federal Food, Drug and

Cosmetic Act, the following statement is included in the Warnings and Precautions section of the device labeling to address testing and reporting of species not listed in the Indications for Use:

The safety and efficacy of antimicrobial drugs, for which antimicrobial susceptibility is tested by this AST device, may or may not have been established in adequate and well controlled clinical trials for treating clinical infections due to microorganisms outside of those found in the indications and usage in the drug label. The clinical significance of susceptibility information in those instances is unknown. The approved labeling for specific antimicrobial drugs provides the uses for which the antimicrobial drug is approved.

2. Matrix Comparison:

Not applicable.

C Clinical Studies:

1. Clinical Sensitivity:

Not applicable.

2. Clinical Specificity:

Not applicable.

3. Other Clinical Supportive Data (When 1. and 2. Are Not Applicable):

Not applicable.

D Clinical Cut-Off:

Not applicable.

E Expected Values/Reference Range:

Table 6: FDA-Recognized Interpretive Criteria for Aztreonam/avibactam

| Organisms | Minimum Inhibitory Concentrations (µg/mL) ^a | | |
|------------------|--|--------------|-----------|
| | Susceptible | Intermediate | Resistant |
| Enterobacterales | ≤4/4 | 8/4 | ≥16/4 |

^aAccording to FDA STIC Webpage, <https://www.fda.gov/drugs/development-resources/fda-recognized-antimicrobial-susceptibility-test-interpretive-criteria>

VIII Proposed Labeling:

The labeling supports the finding of substantial equivalence for this device.

IX Conclusion:

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

To support the implementation of changes to FDA-recognized susceptibility test interpretive criteria (i.e., breakpoints), this submission included a predetermined change control plan (PCCP) with a breakpoint change protocol that was reviewed and accepted by FDA in submission K231994 cleared on August 25, 2023. This referenced protocol addresses future revisions to device labeling in response to breakpoint changes that are recognized on the FDA STIC webpage (<https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm>). The protocol outlined the specific procedures and acceptance criteria that Thermo Fisher Scientific intends to use to evaluate The Sensititre 18–24 hour MIC or Breakpoint Susceptibility System with Aztreonam/avibactam when revised breakpoints for aztreonam/avibactam are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, Thermo Fisher Scientific will update the aztreonam/avibactam device label to include (1) the new breakpoints, (2) an updated performance section after re-evaluation of data in this premarket notification with the new breakpoints, and (3) any new limitations as determined by their evaluation.