510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY

I Background Information:

A 510(k) Number

K212243

B Applicant

bioMérieux, Inc

C Proprietary and Established Names

VITEK 2 AST- Gram Positive Telavancin (≤0.015 - ≥1 µg/mL)

D Regulatory Information

Product Code(s)	Classification	Regulation Section	Panel
LON	Class II	21 CFR 866.1645 - Fully Automated Short-Term Incubation Cycle Antimicrobial Susceptibility System	MI - Microbiology
LTT	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology
LTW	Class II	21 CFR 866.1640 - Antimicrobial susceptibility test powder	MI - Microbiology

II Submission/Device Overview:

A Purpose for Submission:

To obtain a substantial equivalence determination for telavancin testing of Gram-positive cocci on the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test Systems

B Measurand:

Telavancin ≤0.015 - ≥1 µg/mL

C Type of Test:

Automated quantitative or qualitative antimicrobial susceptibility test

III Intended Use/Indications for Use:

A Intended Use(s):

The VITEK 2 AST-Gram Positive Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of *Staphylococcus* spp., *Enterococcus* spp., and *S. agalactiae* to antimicrobial agents when used as instructed.

B Indication(s) for Use:

VITEK 2 AST-Gram Positive Telavancin is designed for antimicrobial susceptibility testing of Gram positive microorganisms and is intended for use with the VITEK 2 and VITEK 2 Compact Systems as a laboratory aid in the determination of *in vitro* susceptibility to antimicrobial agents. VITEK 2 AST-Gram Positive Telavancin is a quantitative test. Telavancin has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial:

Active both *in vitro* and in clinical infections:
Staphylococcus aureus (including methicillin-resistant isolates)
Enterococcus faecalis (vancomycin-susceptible strains only)

The VITEK 2 AST-Gram Positive Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of *Staphylococcus* spp., *Enterococcus* spp., and *S. agalactiae* to antimicrobial agents when used as instructed.

C Special Conditions for Use Statement(s):

Rx - For Prescription Use Only

If the following antibiotic/organism combination is susceptible and vancomycin is intermediate or resistant, perform an alternative method of testing prior to reporting of results:
• [tlv04n] Telavancin: *Staphylococcus aureus*

Due to the occurrence of major errors, perform an alternative method of testing prior to reporting of non-susceptible results for the following antibiotic/organism combination(s):
• [tlv04n] Telavancin: *Enterococcus faecalis*

The ability of the AST card to detect non-susceptible strains with the following combination(s) is unknown because an insufficient number of non-susceptible strains were available at the time of comparative testing:
• [tlv04n] Telavancin: *Staphylococcus aureus, Enterococcus faecalis*

Perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination(s):
• [tlv04n]: Telavancin: *Streptococcus agalactiae*

D Special Instrument Requirements:

VITEK 2 and VITEK 2 Compact Systems using 9.04 software

IV Device/System Characteristics:

A Device Description:

The VITEK 2 AST card is a miniaturized, abbreviated and automated version of the doubling dilution technique for determining the minimum inhibitory concentration (MIC). Each VITEK 2 AST card contains 64 wells. A control well(s) which contain only nutrient medium is resident on all cards. The remaining wells contain premeasured portions of antimicrobials combined with the nutrient media. The isolate to be tested is diluted to a standardized concentration with 0.45% to 0.50% saline before being used to rehydrate the antimicrobial medium within the card. The VITEK 2 System will automatically (or allow operator to manually) dilute the bacterial suspension to prepare an inoculum for susceptibility cards. Then, the VITEK 2 will fill, seal and place the card into the incubator/reader. The VITEK 2 Compact has a manual filling, sealing, and loading operation. The VITEK 2 Systems monitor the growth of each well in the card over a defined period of time. The analysis program determines when a well demonstrates growth based on attenuation of light measured by an optical scanner. This data is used to determine the minimum inhibitory concentration or "MIC" values for the antimicrobial agent. At the completion of the incubation cycle, a report is generated that contains the MIC value along with the interpretive category result for each antimicrobial contained on the card.

VITEK 2 AST-GP Telavancin has the following concentrations of Telavancin in the card: 0.015, 0.125, 0.25 and 0.5 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The MIC result range for the VITEK 2 AST-GP Telavancin is ≤0.015 to ≥1 µg/mL. For all species, the MIC result range indicates that the VITEK 2 system is capable of producing the following MIC results: ≤0.015, 0.03, 0.06, 0.125, 0.25, 0.5 and ≥1 µg/mL for the AST-Gram Positive Telavancin test.

B Principle of Operation:

The VITEK 2 and VITEK 2 Compact Systems utilize automated growth-based detection using attenuation of light measured by an optical scanner. The optics in the systems use visible light to directly measure organism growth within each of the 64 micro-wells. Transmittance optics is based on an initial light reading of a well before significant growth has begun. Every 15 minutes throughout the incubation cycle (defined period of time based on the VITEK 2 card), light transmittance readings of each well determine organism growth by the amount of light that is prevented from passing through the well. At the completion of the incubation period, the MIC values and their associated interpretive category results for each antimicrobial on the test card are displayed in an automatically generated report.

V Substantial Equivalence Information:

A Predicate Device Name(s):

VITEK 2 AST-Gram Positive Dalbavancin (≤ 0.015 - ≥ 1 µg/mL)

B Predicate 510(k) Number(s):

K190616

C Comparison with Predicate(s):

Device & Predicate Device(s):	Device K212243	Predicate K190616
Device Trade Name	VITEK 2 AST-GP Telavancin (≤0.015 - ≥1 µg/mL)	VITEK 2 AST-GP Dalbavancin (≤0.015 - ≥1 µg/mL)
General Device Characteristic Similarities		
Intended Use/Indications For Use	The VITEK 2 AST-Gram Positive Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to determine the susceptibility of *Staphylococcus* spp., *Enterococcus* spp., and *S. agalactiae* to antimicrobial agents when used as instructed.	Same
Test Method	Automated quantitative antimicrobial susceptibility test for use with the VITEK 2 and VITEK 2 Compact Systems to determine *in vitro* susceptibility of microorganisms	Same
Inoculum	Standardized saline suspension of organisms	Same
Test Card	Gram-Positive (AST-GP) Susceptibility Card	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same
Reporting Range	≤0.015 to ≥1 µg/mL	Same
Analysis Algorithm	Growth pattern analysis	Same
General Device Characteristic Differences		
Antimicrobial Agent	Telavancin	Dalbavancin
Antimicrobial Concentrations	0.015, 0.125, 0.25, 0.5	0.0625, 0.125, 0.25, 0.5
Indicated Organisms	*S. aureus* (including methicillin resistant*), E. faecalis* (vancomycin susceptible only)	*S. aureus* (including methicillin resistant), *E. faecalis* (vancomycin susceptible only), *S. agalactiae*

VI Standards/Guidance Documents Referenced:

- CLSI M07-A11: Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard – 11th Edition (January 2018)
- CLSI M100-S30: Performance Standards for Antimicrobial Susceptibility Testing; 30th Informational Supplement (January 2020)
- FDA Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems; Guidance for Industry and FDA (Issued August 28, 2009)

VII Performance Characteristics (if/when applicable):

A Analytical Performance:

1. Precision/Reproducibility:

   Reproducibility testing for the VITEK 2 AST-Gram Positive Telavancin was conducted at three sites (two external and one internal site) using a panel of ten Gram positive organisms consistent with the indications for use (i.e., five isolates of *S. aureus* and five isolates of *E. faecalis*). Each isolate was tested in triplicate, using separate inocula, over three days for a total of 270 data points. Inocula were prepared using both the autodilution and manual dilution methods for testing with the VITEK 2 System. In addition, inocula were prepared by the manual dilution method for testing with the VITEK 2 Compact. The mode of MIC values was determined for each isolate and the reproducibility was calculated based on the number of MIC values that fell within ± 1 doubling dilution of the mode.

   All MIC results were on-scale and within one doubling dilution from the modal MIC value; therefore, only best-case results are reported. The testing resulted in an overall reproducibility of 100% (270/270) when testing with the VITEK 2 System (autodilution and manual dilution methods) and the VITEK 2 Compact System (manual dilution method).

2. Linearity:

   Not Applicable

3. Analytical Specificity/Interference:

   No Applicable

4. Assay Reportable Range:

   Not Applicable

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

   The CLSI recommended QC strains for telavancin, *E. faecalis* ATCC 29212 and *S. aureus* ATCC 29213, were tested a sufficient number of time (i.e., at least 20 times/site) at each testing site using both the VITEK 2 card and broth microdilution reference methods. Both the

automatic dilution and manual dilution methods were used for the VITEK 2 and the manual dilution method was used for VITEK 2 Compact.

Results obtained using the autodilution and the manual dilution methods for VITEK2 and the manual dilution for VITEK 2 Compact QC results are summarized in **Table 1** below. Greater than 95% of the results were within the expected range although trending toward higher MIC values was observed for *E. faecalis* ATCC 29212; QC was determined to be acceptable.

Table 1: Quality Control Results for VITEK 2 (AutoDilution and Manual Dilution Methods) and VITEK 2 Compact (Manual Dilution Method)

Organism	Result Range (µg/mL)	BMD	VITEK 2 Auto-dilution	BMD	VITEK 2 Manual Dilution	BMD	VITEK 2 Compact Manual Dilution
E. faecalis ATCC 29212 Expected 0.03 – 0.12 µg/mL	0.015	-	-	-	-	-	-
	0.03	2	-	2	-	2	-
	0.06	163	-	125	-	126	-
	0.12	48	211	35	162	34	162
	0.25	-	-	-	-	-	-
	0.5	-	2	-	-	-	-
	1	-	-	-	-	-	-
S. aureus ATCC 29213 Expected 0.03 – 0.12 µg/mL	0.015	-	-	-	-	-	-
	0.03	139	-	99	-	99	-
	0.06	76	208	66	164	66	165
	0.12	-	5	-	1	-	-
	0.25	-	-	-	-	-	-
	0.5	-	2	-	-	-	-
	1	-	-	-	-	-	-

BMD – reference broth microdilution

Inoculum Density Check: The DensiCheck Plus was used to standardize the inoculum to a 0.5 McFarland standard. The instrument was standardized daily with all results recorded at each site. Calibration values were within the expected range.

Device Failure: During the performance of the comparative study, there were several instrument processing errors that resulted in loss of AST cards vith the VITEK 2 System. All isolates affected by these errors were retested in accordance with the testing protocol. There were no device failures with the VITEK 2 Compact.

Growth Failure Rate: One clinical isolate of *S. aureus* failed to grow in the VITEK 2 Cards (autodilution). There were no growth failures with VITEK 2 manual dilution or with VITEK 2 Compact.

Purity Check: Purity plates were prepared from the inoculum suspensions. AST results were only reported for pure isolates.

6. Detection Limit:

Not applicable

7. Assay Cut-Off:

Not applicable

B Comparison Studies:

1. Method Comparison with Predicate Device:

Testing of telavancin was performed at three external sites and one internal site. Results obtained with VITEK 2 AST-Gram Positive Telavancin were compared to results obtained with the CLSI broth microdilution reference panel. The MIC result range for the VITEK 2 AST-Gram Positive Telavancin is ≤0.015 to ≥1 µg/mL for all species. The testing conditions for the reference method consisted of the following:

- Medium: Cation Adjusted Mueller Hinton broth supplemented with 0.002% polysorbate 80
- Inoculum: 1 mL of organism suspension standardized to approximate a McFarland 0.5 standard
- Incubation: 35 ± 2°C; 16-20 hours

The VITEK 2 cards were inoculated with test organisms using the auto-dilution method (VITEK 2) and using the manual dilution method (VITEK 2 and VITEK 2 Compact). All test inocula used for the VITEK 2 AST cards and the reference method were standardized using the DensiCHEK Plus instrument.

A total of 771 clinical isolates belonging to all genera were evaluated using autodilution and VITEK 2. Of these isolates, 25% were fresh isolates (tested within seven days from isolation), 25% were recent isolates (tested within one year from isolation) and 50% were stock isolates (no specific time from isolation). The clinical isolates included: 301 isolates of vancomycin susceptible *E. faecalis* and 470 isolates of *S. aureus* (including 161 isolates of MSSA and 309 isolates of MRSA).

A total of 117 challenge isolates were evaluated, including 67 isolates of vancomycin susceptible *E. faecalis* and 50 isolates of *S. aureus* (20 isolates of MSSA and 30 isolates of MRSA).

Clinical and Challenge Data –VITEK 2 Autodilution
The results obtained using the autodilution method of the VITEK 2 from the 888 total isolates (771 clinical isolates and 117 challenge isolates) are summarized in **Table 2**.

Table 2. Performance for Autodilution with VITEK 2

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. NS	No. S	min	maj	vmj
***E. faecalis* (vancomycin susceptible) (Breakpoint: S ≤ 0.25 µg/mL)**													
Clinical	301	265	88.0	300	264	88.0	275	91.4	0	301	N/A	26	0
Challenge	67	66	98.5	67	66	98.5	66	98.5	1	66	N/A	0	
Total	368	331	89.9	367	330	89.9	342	92.9	1	367	N/A	26	0

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. NS	No. S	min	maj	vmj
S. aureus **(MRSA and MSSA combined) (Breakpoint: S ≤ 0.12 µg/mL)**													
Clinical	470	441	93.8	467	438	93.8	465	98.9	0	470	N/A	5	0
Challenge	50	49	98.0	50	49	98.0	49	98.0	0	50	N/A	1	0
Total	520	490	94.2	517	487	94.2	514	98.8	0	520	N/A	6	0

N/A - Not applicable due to only a susceptible breakpoint for Telavancin

EA – Essential Agreement
CA – Category Agreement
EVAL – Evaluable Isolates
NS – Non-Susceptible Isolates
min – minor errors
maj – major errors
vmj – very major errors
S – Susceptible Isolates

Essential agreement (EA) occurs when the result of the reference method and that of the VITEK 2 AST-Gram Positive Telavancin 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 VITEK 2 AST-Gram Positive Telavancin or results 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 provided by the VITEK 2 AST-Gram Positive Telavancin.

For *S. aureus* (MSSA and MRSA combined) evaluated using VITEK 2 and autodilution, the overall EA and CA were acceptable at 94.2% and 98.9%, respectively (**Table 2**), with six susceptible isolates providing non-susceptible results (major errors). For MSSA, the EA and CA were 95.6% and 99.5%, respectively, with one major error; for MRSA, the EA and CA were 93.5% and 98.5%, respectively with five major errors. The results for *S. aureus* were acceptable.

For vancomycin susceptible *E. faecalis* evaluated using VITEK 2 and autodilution, the overall EA and CA were acceptable at 89.9% and 92.9%, respectively (**Table 2**). Of the 367 susceptible isolates, 26 (7.1%) provided non-susceptible MICs (major errors). All of the major errors occurred with clinical isolates. Five of the major errors were within essential agreement with the reference method; due to the lack of an intermediate breakpoint, these five major errors were considered acceptable, and the major error rate was adjusted to 5.7% which is still higher than the acceptable rate of major errors. To address the major errors observed with *E. faecalis*, the following limitation was included in the device labeling:

Due to the occurrence of major errors, perform an alternative method of testing prior to reporting of non-susceptible results for the following antibiotic/organism combination:
- *[tlv04n] Telavancin: Enterococcus faecalis*

To provide clarity on the calculation of the adjusted major error rate, the following footnote was added to the performance table in th device labeling:

Five major errors for Enterococcus faecalis were within essential agreement with the reference method; due to the lack of an intermediate breakpoint these five major errors were considered acceptable and the major error rate is adjusted to 5.7% which will still require retesting of non-susceptible strains with an alternate method.

Challenge Data –VITEK 2 and VITEK 2 Compact Manual Dilution
The 117 challenge isolates were also evaluated with the manual dilution options of the VITEK 2 and VITEK 2 Compact systems (summarized in **Table 3**).

Table 3. Performance for Manual Dilution with VITEK 2 and VITEK 2 Compact

	Tot	EA N	EA %	Eval Tot	Eval EA N	Eval EA %	CA Tot	CA %	No. NS	No. S	min	maj	vmj
***E. faecalis* (Breakpoint: S ≤ 0.25 µg/mL)**													
VITEK 2	67	66	98.5	67	66	98.5	67	100.0	1	66	N/A	0	0
VITEK 2 Compact	67	64	95.5	67	64	95.5	65	97.0	1	66	N/A	2	0
***S. aureus* (Breakpoint: S ≤ 0.12 µg/mL)**													
VITEK 2	50	49	98.0	49	49	100.0	50	100.0	0	50	N/A	0	0
VITEK 2 Compact	50	50	100.0	48	48	100.0	50	100.0	0	50	N/A	0	0

N/A - Not applicable due to only a susceptible breakpoint for Telavancin

The overall performance of VITEK 2 when using the manual dilution method with *E. faecalis* challenge isolates was acceptable with an EA of 98.5%, a CA of 100%, and zero major or very major errors. The overall performance of VITEK 2 when using the manual dilution method with *S. aureus* challenge isolates was also acceptable with an EA of 98.0%, a CA of 100%, and zero major or very major errors.

The overall performance of VITEK 2 Compact with *E. faecalis* challenge isolates showed an EA of 95.5%, a CA of 97.0%, and zero (0) very major errors. Of the 66 susceptible isolates, two (3.0%) provided non-susceptible MICs (major errors), which is not acceptable, as described and addressed in the limitation statement above. The overall performance of VITEK 2 Compact with *S. aureus* challenge isolates was acceptable with an EA of 100%, a CA of 100%, and zero major or very major errors.

No non-susceptible isolates of *S. aureus* were evaluated in the comparative study and only a single non-susceptible isolate of *E. faecalis* was tested. To address the lack of information regarding performance with non-susceptible strains, the following limitation was added to the device labeling:

The ability of the AST card to detect non-susceptible strains with the following combination(s) is unknown because an insufficient number of non-susceptible strains were available at the time of comparative testing:
• [tlv04n] Telavancin: Staphylococcus aureus, Enterococcus faecalis

In addition to evaluating results obtained with *S. aureus* and *E. faecalis*, 55 isolates of *S. agalactiae* were tested with the autodilution method and 27 isolates of *S. agalactiae* were tested with the manual dilution method. However, performance of telavancin with this species was not acceptable with either the VITEK 2 or VITEK 2 Compact. The following limitation was added to the device labeling:

Perform an alternative method of testing prior to reporting of results for the following antibiotic/organism combination(s):
• [tlv04n]: Telavancin: Streptococcus agalactiae

As required under 511A(b)(2)(C)(ii)(I) of the Federal Food, Drug and Cosmetic Act, the following statement is included in the Precautions section of the device labeling to address testing and reporting of non-indicated species:

Per the FDA-Recognized Susceptibility Test Interpretive Criteria website, 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.

Trending

A trending analysis was conducted using the combined data (clinical and challenge) obtained from the VITEK 2 autodilution method for each species. This trending calculation analyzes device MIC values that are determined to be one or more doubling dilutions lower or higher than the reference method. MIC values that are off-scale for both the reference and device are not considered in the trending analysis. Species for which the difference between the percentage of isolates with higher or lower MIC values was ≥ 30% with a statistically significant confidence interval were considered to have evidence of trending and is addressed in the labeling.

Table 4. Trending Observed for *E. faecalis* and *S. aureus* with VITEK 2 Autodilution

Organism	Total Evaluable for Trending	≥ 1 Dilution lower No. (%)	Exact No. (%)	≥ 1 Dilution Higher No. (%)	Percent Difference (CI)	Trending Noted
E. faecalis	367	16 (4.4)	145 (39.5)	206 (56.1)	51.8% (46.0 to 57.0)	Yes
S. aureus	517	2 (0.4)	172 (33.3)	343 (66.3)	66.0% (61.7 to 69.9)	Yes

A trend toward higher MIC values was observed for *E. faecalis* and *S. aureus* (**Table 4**). To address the observed trending, the following footnote was added to the performance table in the device labeling:

VITEK 2 AST-Gram Positive Telavancin MIC values tended to be in exact agreement or at least one doubling dilution higher when testing E. faecalis and S. aureus compared to the CLSI reference broth microdilution method.

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 5. FDA-Recognized Interpretive Criteria for Telavancin

Organisms	Interpretive Criteria (µg/mL)[a]		
	S	I	R
Staphylcoccus aureus (including methicillin resistant)	≤0.12	-	-
Enterococcus faecalis (vancomycin susceptible only)	≤0.25	-	-

[a] As noted on the FDA STIC Website.

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 breakpoint change protocol that was reviewed and accepted by FDA. This 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 bioMérieux intends to use to evaluate the VITEK 2 AST-GP Telavancin when revised breakpoints for telavancin are published on the FDA STIC webpage. The breakpoint change protocol included with the submission indicated that if specific criteria are met, bioMérieux will update the telavancin 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.