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

A. 510(k) Number:

K190616

B. Purpose for Submission:

To obtain a substantial equivalence determination for dalbavancin for testing of Gram-positive organisms on the VITEK 2 and VITEK 2 Compact Antimicrobial Susceptibility Test (AST) Systems

C. Measurand:

Dalbavancin ≤0.015 – ≥1 µg/mL for *Staphylococcus aureus* (including methicillin-resistant isolates), *Enterococcus faecalis* (vancomycin-susceptible isolates only), and *Streptococcus agalactiae*.

D. Type of Test:

Automated quantitative or qualitative antimicrobial susceptibility test.

E. Applicant:

bioMérieux, Inc.

F. Proprietary and Established Names:

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

G. Regulatory Information:

1. Regulation section:

   21 CFR 866.1645: Fully Automated Short-Term Incubation Cycle Antimicrobial Susceptibility System

2. Classification:

   Class II

3. Product code(s):

   LON – Fully automated short-term incubation cycle antimicrobial susceptibility system
   LTW – Susceptibility Test Cards, Antimicrobial
   LTT – Panels, Test, Susceptibility, Antimicrobial

4. Panel:

   Microbiology, 83

H. Intended Use/Indications for Use:

1. Intended Use (s):

   The VITEK 2 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 clinically significant Gram positive microorganisms to antimicrobial agents when used as instructed.

2. Indications for Use:

   VITEK 2 AST-Gram Positive Dalbavancin 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 Dalbavancin is a quantitative test. Dalbavancin 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 isolates only)
   Streptococcus agalactiae

   The VITEK 2 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 clinically significant Gram positive microorganisms to antimicrobial agents when used as instructed.

3. Special conditions for use statement(s):

   For Prescription Use Only

   Limitations:

   1. 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:

      Dalbavancin: *Staphylococcus aureus*

   2. 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:

      Dalbavancin: *Staphylococcus aureus*, *Streptococcus agalactiae*, *Enterococcus faecalis* (vancomycin-susceptible)

4. Special instrument requirements:

   VITEK 2 and VITEK 2 Compact Systems, VITEK 2 Systems (PC) version 10.1 or higher

I. 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 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 anti-microbial 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 Dalbavancin has the following concentrations in the card: 0.0625, 0.125, 0.25, and 0.5 µg/mL (equivalent standard method concentration by efficacy in µg/mL). The Dalbavancin MIC result range for the VITEK 2 is ≤0.015 – ≥1 µg/mL for *Staphylococcus aureus, Enterococcus faecalis, Streptococcus agalactiae.* For all species, the VITEK 2

system is capable of reporting the following MIC results: ≤0.015, 0.03, 0.06, 0.125, 0.25, 0.5 and ≥1 µg/mL for the AST-GP Dalbavancin test.

J. Substantial Equivalence Information:

1. Predicate device name(s):

   VITEK 2 AST-GP Ceftaroline

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

   K141149

3. Comparison with predicate:

Table 1: Comparison with Predicate Device

Similarities		
Item	**Device: VITEK 2 AST-GP Dalbavancin (K190616)**	**Predicate Device: VITEK 2 AST-GP Ceftaroline (K141149)**
Intended Use/Indications for Use	VITEK 2 AST-Gram Positive Dalbavancin 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 Dalbavancin is a quantitative test. Dalbavancin has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial. **Active *in vitro* and in clinical infections** *Staphylococcus aureus* (including methicillin-resistant isolates) *Enterococcus faecalis* (vancomycin-susceptible isolates only) *Streptococcus agalactiae* The VITEK 2 Gram-positive Susceptibility Card is intended for use with the VITEK 2 Systems in clinical laboratories as an *in vitro* test to	VITEK 2 Gram Positive Ceftaroline 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 Gram Positive Ceftaroline is a quantitative test. Ceftaroline has been shown to be active against most strains of the microorganisms listed below, according to the FDA label for this antimicrobial. **Active *in vitro* and in clinical infections** *Staphylococcus aureus* (including methicillin-susceptible and -resistant isolates) The VITEK 2 Antimicrobial Susceptibility Test (AST) is intended for use with the VITEK 2 Systems for the automated quantitative or qualitative susceptibility testing of isolated colonies for the most clinically significant aerobic gram-negative

Similarities		
Item	**Device: VITEK 2 AST-GP Dalbavancin (K190616)**	**Predicate Device: VITEK 2 AST-GP Ceftaroline (K141149)**
	determine the susceptibility of *Staphylococcus* spp., *Enterococcus* spp., and *S. agalactiae* to antimicrobial agents when used as instructed.	bacilli, *Staphylococcus* spp., *Enterococcus* spp., *Streptococcus* spp. and clinically significant yeast.
Test Method	Automated quantitative antimicrobial susceptibility test for use with the VITEK 2 and VITEK 2 Compact Systems to determine the *in vitro* susceptibility of microorganisms	Same
Inoculum	Saline suspension of organism	Same
Test Card	Gram Positive (AST-GP) Susceptibility Card	Same
Instrument	VITEK 2 and VITEK 2 Compact Systems	Same
Analysis Algorithm	Growth pattern analysis	Same

Differences		
Antimicrobial Agent	Dalbavancin	Ceftaroline
Antimicrobial Concentrations	0.0625, 0.125, 0.25, 0.5 µg/mL	0.25, 0.5, 1, 2 µg/mL
Base Broths	GP13	GP1

K. Standard/Guidance Documents Referenced (if applicable)

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

- CLSI M07-A10, "Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically; Approved Standard-Ninth Edition" Vol. 35 No. 2 (January 2015)

- CLSI M100, "Performance Standards for Antimicrobial Susceptibility Testing"; Twenty-eighth Edition (January 2018)

L. Test Principle:

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 uses 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 measures 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.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

A reproducibility study for the VITEK 2 AST-GP card with Dalbavancin was conducted at three external clinical sites using a panel of ten isolates of Gram-positive microorganisms consistent with the indications for use. Testing was performed on three separate days and in triplicate for a total of 270 data points. The isolates tested in the reproducibility study included five *Staphylococcus aureus* and five *Enterococcus faecalis* isolates. Inocula were prepared using both the auto-dilution and manual dilution methods for testing in the VITEK 2 System. In addition, inocula were prepared by the manual dilution method only for use with the VITEK 2 Compact. The mode MIC value was determined and the reproducibility was calculated based on MIC values that fell within +/- one doubling dilution from the mode MIC value. The data was analyzed taking into consideration best case and worst case scenarios as described in the Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems. All reproducibility performance results were considered acceptable; however, 7% of the total isolates were off-scale. The reproducibility performance of the on-scale isolates is presented in Table 2.

Table 2: Reproducibility Performance

VITEK 2		VITEK 2 Compact
Auto-Dilution	**Manual Dilution**	**Manual Dilution**
99.63%	99.63%	97.41%

b. Linearity/assay reportable range:

Not applicable

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

Quality Control (QC) Testing

The CLSI recommended QC organisms (*Enterococcus faecalis* ATCC 29212 and *Staphylococcus aureus* ATCC 29213) were tested using both the VITEK 2 card and the reference method at each site. Both the automatic dilution and manual dilution methods were used for the VITEK 2 and the manual dilution method was used for the VITEK 2 Compact.

As shown in Table 3, both the auto-dilution and the manual dilution methods for VITEK 2 and the manual dilution for VITEK 2 Compact QC results were within the expected range >95% of the time.

Table 3: Quality Control Summary Results for VITEK 2 (Auto-Dilution and Manual Dilution Methods) and VITEK 2 Compact (Manual Dilution Method)

Organism	VITEK 2 Result Range	MIC Result (µg/mL)	VITEK 2 Auto Dilution	Ref	VITEK 2 Manual Dilution	Ref	VITEK 2 Compact Manual Dilution	Ref
E. faecalis ATCC 29212 Expected Result: 0.03-0.125 µg/mL		≤ 0.008						
	*	0.015			1		4	
	*	0.03	181	72	181	66	182	65
	*	0.06	25	90	9	83	2	81
	*	0.125		37		35		35
	*	0.25		7		7		7
	*	0.5						
	*	1						
		2						
		≥ 4						
S. aureus ATCC 29213 Expected Result: 0.03-0.125 µg/mL		≤ 0.008						
	*	0.015		1		1		1
	*	0.03	134	123	141	113	147	113
	*	0.06	65	41	44	38	39	38
	*	0.125	1	35		33		33
	*	0.25		1		1		1
	*	0.5	1		1			
	*	1						
		2						
		≥ 4						

***** denotes MIC result range produced by AST-GP Dalbavancin test
Ref, CLSI reference method

Inoculum Density Control

The DensiCHEK 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.

Purity Check
A purity check of all organisms was performed on the dilution tube used to prepare the VITEK 2 card inoculum. Only those cultures that were pure were evaluated in the study.

Growth Failure Rate
A total of 593 clinical isolates were evaluated. All 593 isolates grew in the VITEK 2 AST-GP Dalbavancin test. Complete test results are available for 593 isolates.

A challenge set of 75 isolates was evaluated at one site. All 75 challenge organisms grew in the VITEK 2 GP card with Dalbavancin using both the auto-dilution and manual dilution methods for the VITEK 2 and manual inoculation for the VITEK 2 Compact System.

A total of 668 VITEK 2 AST results were available.

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:

Testing of Dalbavancin on the VITEK 2 AST-Gram Positive card was performed at three external sites and an internal site. Results obtained with the bioMérieux VITEK 2 AST-Gram Positive card with Dalbavancin were compared to results obtained with the CLSI broth microdilution reference panel. The MIC result range for the VITEK 2 AST-GP Dalbavancin is ≤0.015 – ≥1 µg/mL for all species. The reference panel contained two-fold serial dilutions with a range of ≤0.008 to ≥8 µg/mL. The testing conditions for the reference method consisted of the following:

- Medium – Cation Adjusted Mueller Hinton broth with appropriate dilutions of antimicrobial solution added
- Inoculum – Direct colony suspension
- Incubation – 35°C ambient air incubator; 20-24 hours *Streptococci*, 16-20 hours *Staphylococci* and *Enterococci*

The VITEK 2 AST cards were inoculated with test organisms using the auto-dilution method (VITEK 2 System) and using the manual dilution method (VITEK 2 System 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 593 clinical isolates were evaluated. The majority of isolates were recently isolated from clinical specimen (559 isolates, 94.3%). The remainder were stock isolates (34 isolates, 5.7%).

A total of 75 challenge organisms (41 *Staphylococcus aureus*, 22 *Enterococcus faecalis*, 12 *Streptococcus agalactiae*) were evaluated at one site. The challenge set was tested with the auto-dilution and manual dilution options of the VITEK 2 System and with the manual dilution method on the VITEK 2 Compact System.

The combined data set of clinical and challenge isolates included 668 AST results (346 *Staphylococcus aureus*, 260 *Enterococcus faecalis*, 62 *Streptococcus agalactiae*). A total of 4 (0.6%) non-susceptible isolates were tested among the clinical (n=593) and challenge (n=75) isolates.

The overall performance using the auto-dilution method of the VITEK 2 System demonstrated an EA of 98.1% and a CA of 100%. There were no very major errors and no major errors. With *Staphylococcus aureus* isolates, performance was acceptable with an EA of 97.7% and a CA of 100%. With *Enterococcus faecalis* isolates, performance was acceptable with an EA of 99.6% and a CA of 100%. With *Streptococcus agalactiae* isolates, performance was acceptable with an EA of 93.5% and a CA of 100%. The performance based on combined clinical and challenge data was acceptable. The overall performance is shown in Table 4.

Table 4. Performance of Clinical and Challenge Isolates, VITEK 2 Auto-Dilution Method

Organism Type	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#NS	Min	Maj	Vmj
E. faecalis												
Clinical	238	237	99.6	210	209	99.5	238	100.0	2	N/A	0	0
Challenge	22	22	100	15	15	100	22	100.0	1	N/A	0	0
Combined	**260**	**259**	**99.6**	**225**	**224**	**99.6**	**260**	**100.0**	**3**	**N/A**	**0**	**0**
S. aureus												
Clinical	305	298	97.7	299	292	97.7	305	100.0	1	N/A	0	0
Challenge	41	40	97.6	41	40	97.6	41	100.0	0	N/A	0	0
Combined	**346**	**338**	**97.7**	**340**	**332**	**97.6**	**346**	**100.0**	**1**	**N/A**	**0**	**0**
S. agalactiae												
Clinical	50	46	92.0	7	3	42.9	50	100.0	0	N/A	0	0
Challenge	12	12	100	0	0	-	12	100.0	0	N/A	0	0
Combined	**62**	**58**	**93.5**	**7**	**3**	**42.9**	**62**	**100.0**	**0**	**N/A**	**0**	**0**
All species												
Clinical	593	581	98.0	516	504	97.7	593	100.0	3	N/A	0	0
Challenge	75	74	98.7	56	55	98.2	75	100.0	1	N/A	0	0
Combined	**668**	**655**	**98.1**	**572**	**559**	**97.7**	**668**	**100.0**	**4**	**N/A**	**0**	**0**

EA – Essential Agreement (± 1 dilution) **Min** – minor discrepancies
CA – Category Agreement **Maj** – major discrepancies
Eval – Evaluable isolates **Vmj** – very major discrepancies
NS – Non-susceptible isolates **N/A** – Not applicable

Essential agreement (EA) occurs when the result of the reference method and that of the VITEK card 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 card. Category agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation provided by the VITEK card.

Challenge Data –Manual Dilution

The challenge data set was also evaluated at one site with the manual dilution options of the VITEK 2 System and VITEK 2 Compact System. The performance was acceptable. Overall performance is shown in Table 5, and performances with *E. faecalis, S. aureus* and *S. agalacticae* isolates are shown in Table 6, Table 7 and Table 8, respectively.

Table 5. Performance of Challenge Isolates, VITEK 2 and VITEK 2 Compact Manual Dilution – All Organisms

System	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#NS	Min	Maj	Vmj
VITEK 2	75	75	100	56	56	100	75	100	1	N/A	0	0
VITEK 2 Compact	75	74	98.7	54	53	98.1	75	98.7	1	N/A	0	0

Table 6. Performance of Challenge Isolates, VITEK 2 and VITEK 2 Compact Manual Dilution – *E. faecalis*

System	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#NS	Min	Maj	Vmj
VITEK 2	22	22	100	15	15	100	22	100	1	N/A	0	0
VITEK 2 Compact	22	22	100	13	13	100	22	100	1	N/A	0	0

Table 7. Performance of Challenge Isolates, VITEK 2 and VITEK 2 Compact Manual Dilution – *S. aureus*

System	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#NS	Min	Maj	Vmj
VITEK 2	41	41	100	41	41	100	41	100	0	N/A	0	0
VITEK 2 Compact	41	40	97.6	41	40	97.6	41	97.6	0	N/A	0	0

Table 8. Performance of Challenge Isolates, VITEK 2 and VITEK 2 Compact Manual Dilution – *S. agalactiae*

System	EA Total	EA N	EA %	Eval EA Total	Eval EA N	Eval EA %	CA N	CA %	#NS	Min	Maj	Vmj
VITEK 2 System												
VITEK 2	12	12	100	0	0	-	12	100	0	N/A	0	0
VITEK 2 Compact												
COMPACT	12	12	100	0	0	-	12	100	0	N/A	0	0

MIC Trends:

An analysis of trending was conducted using the combined clinical and challenge data for each organism group. This trending calculation considers MIC values that are determined to be one or more doubling dilutions lower or higher compared to the reference method regardless of whether the device MIC values are on-scale. Results that are not clearly determined to be at least one dilution lower, at least one dilution higher or in exact agreement with the CLSI reference method are not considered in the trending analysis.

Trending results were stratified by species to assess species-related trends. Species for which the difference between the percentage of isolates with higher or lower readings was ≥30 with a statistically significant confidence interval were considered to show evidence of trending. There was no trending noted for *E. faecalis, S. aureus and S. agalactiae*.

b. Matrix comparison:

Not applicable

3. Clinical studies:

Not applicable

4. Clinical cut-off**:**

Not applicable

5. Expected values/Reference range:

Table 9: Interpretive Criteria for Dalbavancin (FDA STIC Webpage* and CLSI M100)

Organism	FDA Recognized Interpretive Criteria for Dalbavancin MIC (µg/mL)		
	S	I	R
Staphylococcus aureus (including methicillin-resistant isolates)	≤0.25	-	-
Enterococcus spp. (vancomycin-susceptible isolates only)	≤0.25	-	-
Streptococcus spp. β-Hemolytic Group	≤0.25	-	-

* FDA STIC Webpage
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm410971.htm

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.

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 Gram-positive Susceptibility Card when revised breakpoints for dalbavancin 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 dalbavancin 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.