DIAGNOSTIC-THERAPY COMBINATION: BIOMERIEUX SUPPORTIVE DIAGNOSTICS SOLUTIONS

to accompany the clinical development and the safe prescription of anti-infectives

USE OF AN ENABLING RAPID DIAGNOSTIC IN ATTACK, A RECENT, PATHOGEN-FOCUSED PHASE 3 STUDY

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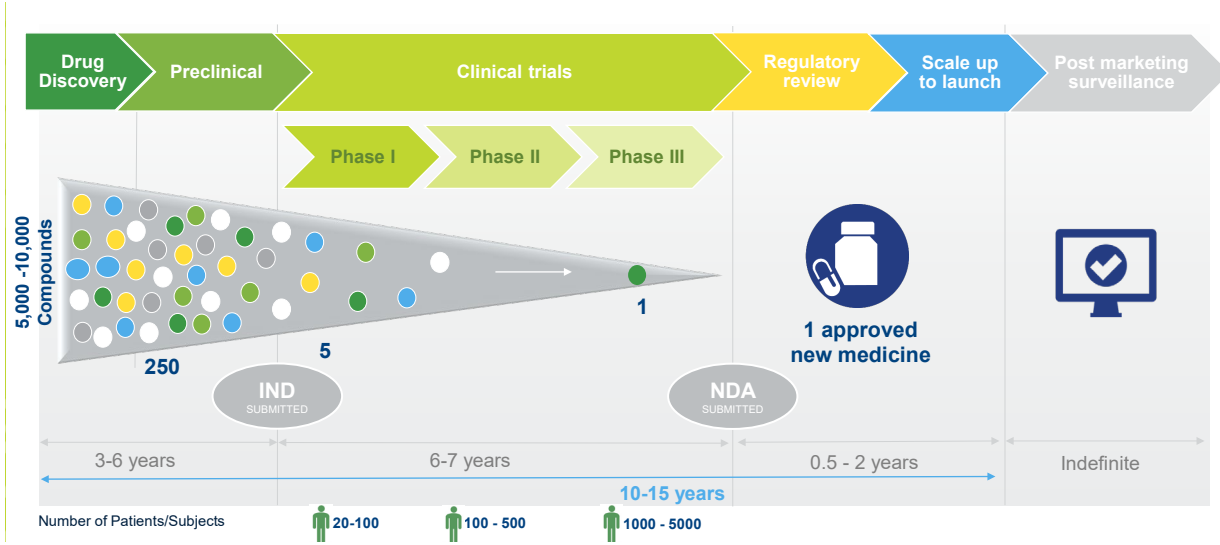
PIONEERING DIAGNOSTICS

THE VALUE OF DIAGNOSTIC FROM DRUG CLINICAL DEVELOPMENT TO COMMERCIALIZATION



CLINICAL TRIALS

COMMERCIALIZATION

Pharma challenges & expectations

Clinical Trials are Long, Costly, and could Fail
Maximize the trial probability of success while optimizing time & cost

Personalized Medicine is crucial for innovative drugs, : "The Right treatment for the Right Patient at the Right Moment and with the Right Dose."

The value of Diagnostic

Optimize clinical trial by selecting the optimal patient population leading to an increased probability of trial success, as well as time-savings and cost-effectiveness by limiting unnecessary patient drug exposure.

Ensure the most appropriate choice of drug in a given context to improve the chances of positive patient outcome while avoiding/limiting undesirable side effects leading to safe drug adoption and prescription

BIOFIRE®

NEPHROCHECK®

ETEST®

VITEK® 2

VIDAS® 3

BIOMÉRIEUX

DIAGNOSTIC-THERAPY COMBINATION
KEY BENEFITS

FOR THE PATIENTS

- ✓ Stratification leading to the prescription of the **right therapy for the right patient.**
- ✓ **Quicker selection of the optimal therapy.**
- ✓ **Improved patient outcomes** and reduced side effects.
- ✓ **Deeper understanding** of the disease & medical decision.

FOR PHARMA COMPANIES

- ✓ **Safer drug prescription,** helping to protect drug efficacy & prevent drug misuse.
- ✓ **Increased probability of clinical trial success** as the drug is prescribed to a subpopulation likely to positively respond to the treatment.
- ✓ **Opportunity to get a premium reimbursement** as a **higher medical value** is delivered to patients.

FOR IVD COMPANIES

- ✓ **Increased recognition** of the high medical value of IVD solutions.
- ✓ **Co-development strategy** for early & timely diagnostic availability.
- ✓ **Co-adoption strategy** for enhanced market access: joint medical education & promotion, synergies for reimbursement…
- ✓ Contribution to the **overall control of the healthcare spending** as diagnostic supports personalized medicine.

CLINICAL TRIAL OPTIMIZATION & COHORT ENRICHMENT
BIOFIRE *as* SUPPORTIVE DIAGNOSTICS

Narrow spectrum/pathogen specific antibiotic

Example of an Acinetobacter specific antibiotic

Clinical Trial Optimization

Potential subjects

Hospitalized adults with respiratory symptoms

6 to 10 patients **screened**

Rapid screening assay + Positive result = inclusion criteria
Acinetobacter baumannii

1h

Eligible patients with confirmed infection

Patients infected by Acinetobacter baumannii

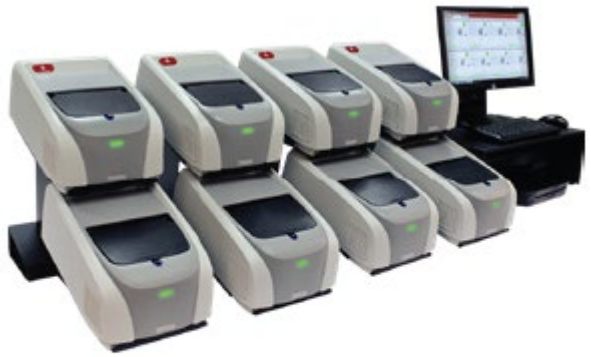
1 patient **enrolled**

Enrollment in the clinical trial

FOCUS ON THE BIOFIRE PNEUMONIA PANEL

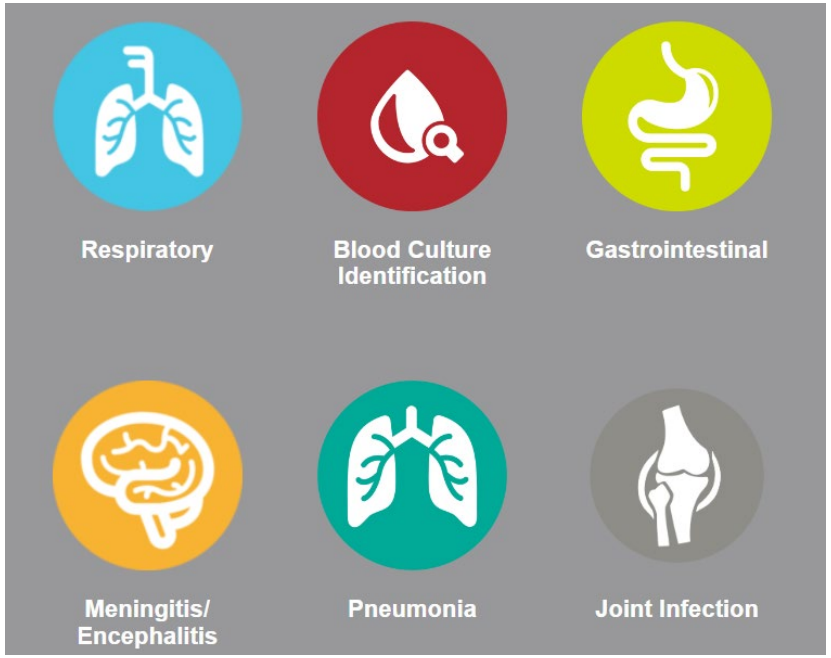
BIOFIRE® INSTRUMENTS & PANELS

- **FDA-cleared and CE-marked**, **direct-from-sample, multiplex PCR system** that integrates sample preparation, amplification, and detection into one closed system
- **~2 minutes of hands-on time** and **total run time of ~ 45-65 min**
- Random access, around-the-clock performance
- No sample pre-processing required



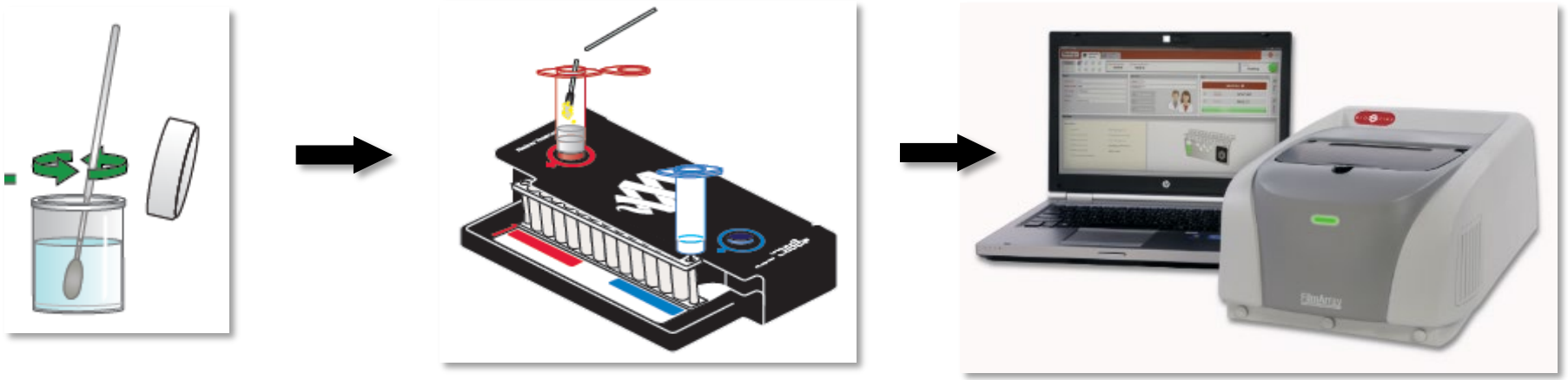
BIOFIRE® FILMARRAY® 2.0
FDA cleared
and CE-marked

BIOFIRE® FILMARRAY® TORCH
FDA cleared
and CE-marked



THE BIOFIRE® FILMARRAY® PNEUMONIA PANEL

- The BIOFIRE® FILMARRAY® instrument **integrates** sample preparation, amplification, detection, and analysis **into one simple system**.



FAST AND EASY
Two minutes of hands-on time
Run time of ~1 hour

ACCURATE
overall sensitivity
96.2 % (BAL) & 96.3 % (sputum)
overall specificity
98.3% (BAL) & 97.2% (sputum)

COMPREHENSIVE
Multiplex PCR
Simultaneously tests for 26 respiratory pathogens
+ 7 resistance markers

BIOFIRE® PNEUMONIA PANEL (PN)

Bacteria

Semi – Quantitative Log Bins

15

- *Acinetobacter calcoaceticus-baumannii* complex
- *Enterobacter cloacae*
- *Escherichia coli*
- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Klebsiella pneumoniae* group
- *Haemophilus influenzae*
- *Moraxella catarrhalis*
- *Proteus* spp.
- *Pseudomonas aeruginosa*
- *Serratia marcescens*
- *Staphylococcus aureus*
- *Streptococcus pneumoniae*
- *Streptococcus pyogenes*
- *Streptococcus agalactiae*

Atypical Bacteria

Qualitative

3

- *Legionella pneumophila*
- *Mycoplasma pneumoniae*
- *Chlamydia pneumoniae*

Viruses

8

- Influenza A
- Influenza B
- Adenovirus
- Coronavirus
- Parainfluenza virus
- Respiratory Syncytial virus
- Human Rhinovirus/Enterovirus
- Human Metapneumovirus

Resistance markers

7

- *mecA*/*mecC* and MREJ
- KPC
- NDM
- Oxa48-like
- CTX-M
- VIM
- IMP

OUS: MERS CoV (Pneumonia *Plus*)
US: No MERS CoV (Pneumonia)

INTENDED USE

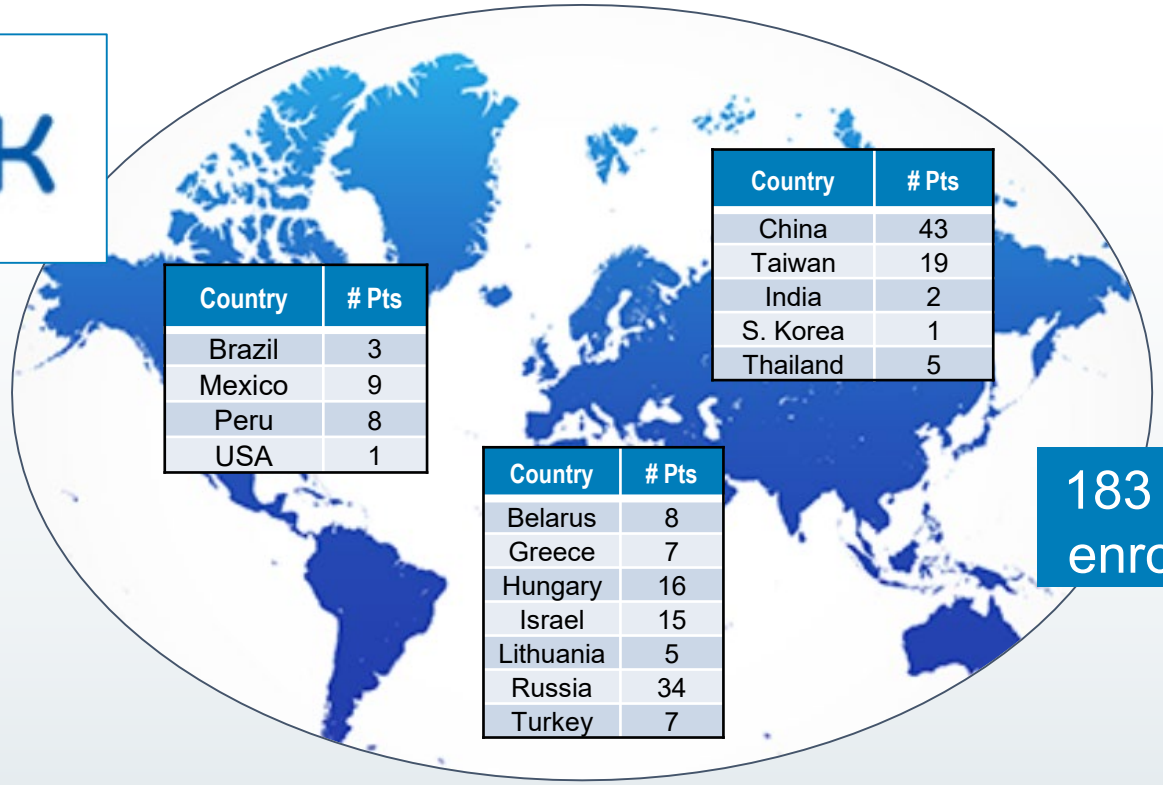
- To aid in diagnosis of lower respiratory tract infections
- For use on patients w/ signs and/or symptoms of lower respiratory tract infection. Including, CAP, HCAP, HAP and VAP
- Identifies relevant viruses, bacteria, and antimicrobial resistance genes, directly from Sputum (including endotracheal aspirates) and BAL (including mini-BAL) samples
- Common bacterial analytes are reported with semi-quantitative results

PIONEERING DIAGNOSTICS

Biofire Pneumonia Panel (BPP) in ATTACK

- ATTACK was a global Phase 3 study to compare the safety and efficacy of sulbactam-durlobactam vs. colistin for the treatment of carbapenem-resistant *Acinetobacter baumannii calcoaceticus* complex (ABC) infections
  - 85 sites activated, 71 sites screened patients, 59 sites randomized patients

ATTACK



Country	# Pts
Brazil	3
Mexico	9
Peru	8
USA	1

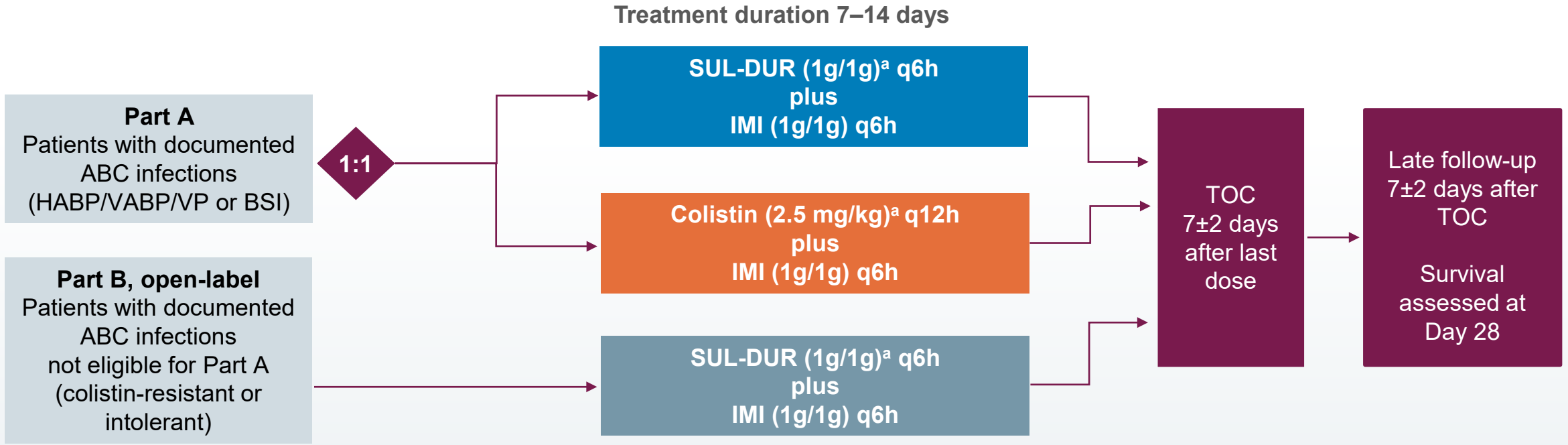
Country	# Pts
China	43
Taiwan	19
India	2
S. Korea	1
Thailand	5

Country	# Pts
Belarus	8
Greece	7
Hungary	16
Israel	15
Lithuania	5
Russia	34
Turkey	7

183 patients from 16 countries enrolled in m-MITT population

ATTACK Study Design

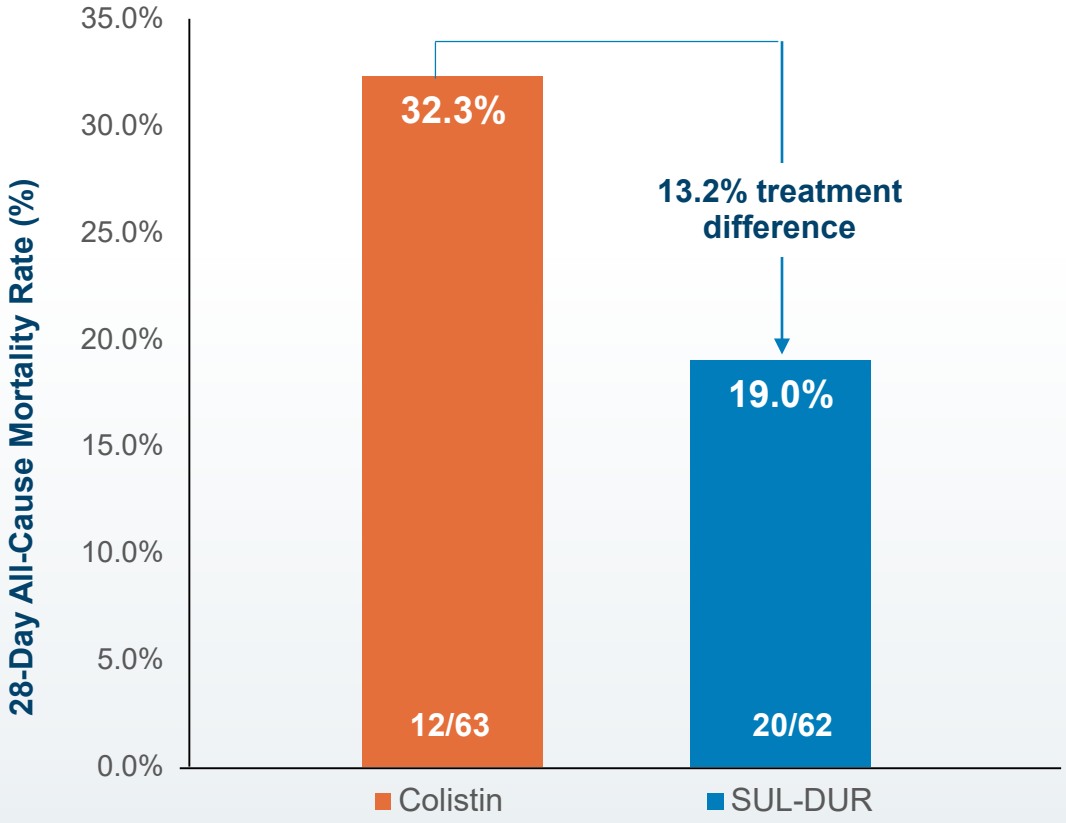
- ATTACK was a Phase 3, multinational, randomised, controlled, noninferiority trial conducted to evaluate the efficacy and safety of SUL-DUR versus colistin, both in combination with imipenem/cilastatin as background therapy, for patients with serious infections due to ABC, including CRABC strains



This trial is registered at ClinicalTrials.gov: NCT03894046.
[a]SUL-DUR dosing was adjusted for renal function. Colistin dosing was adjusted to ideal body weight and renal function. A single colistin loading dose of 2.5 to 5 mg/kg given intravenously over 3 to 6 minutes (or according to standard of care) was administered on Day 1 for patients who had not received prior colistin therapy.
BSI, bloodstream infection; CRABC, carbapenem-resistant *Acinetobacter baumannii-calcoaceticus* complex; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem/cilastatin; q×h, every × hours; TOC, test of cure; VABP, ventilator-associated bacterial pneumonia; VP, ventilated pneumonia.

Achieved Primary Efficacy and Safety Endpoints

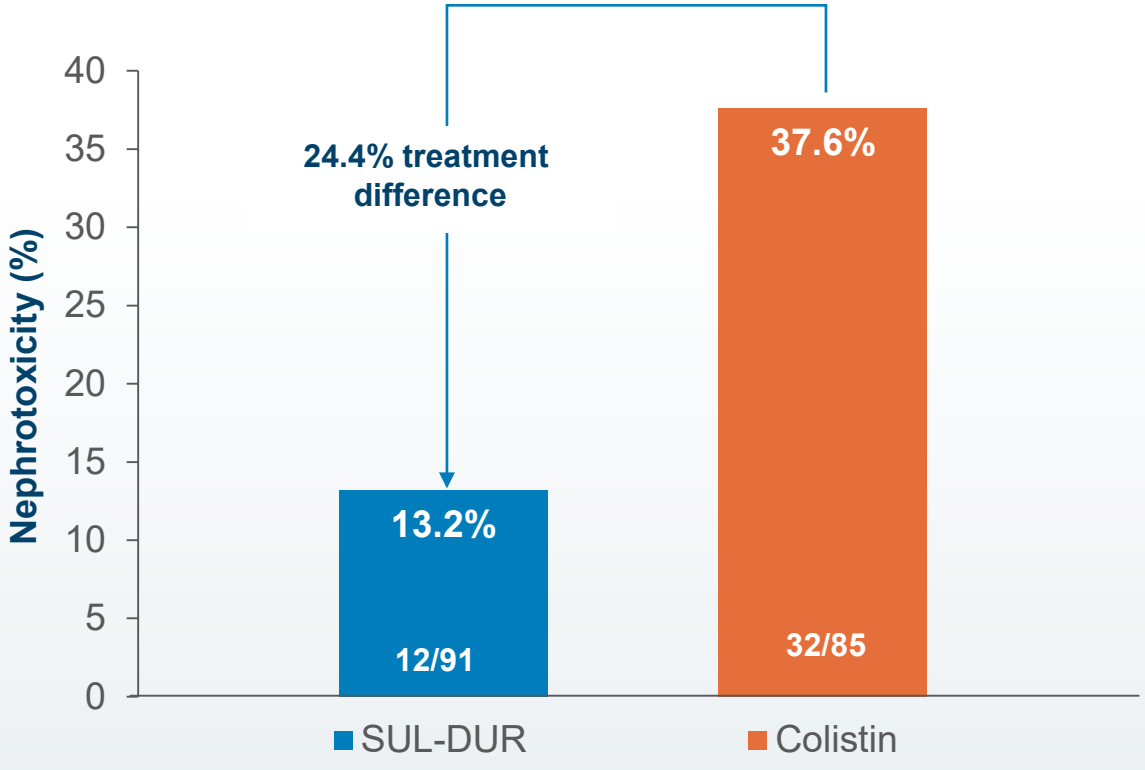
SUL-DUR was non-inferior to colistin on 28-day all-cause mortality



Noninferiority margin is +20%

Excludes participants who withdrew consent.
Participants with missing survival status were treated as a death.

SUL-DUR had statistically significant reduction in nephrotoxicity vs. colistin



Excludes patients with chronic haemodialysis at baseline. Note: If patients had multiple RIFLE events during post-baseline visits, the patient was counted only once at the highest severity. Please see ECCMID abstract 02145 for additional safety data.
RIFLE measured by creatinine level or glomerular filtration rate. A chi-square test was used to determine statistical significance between treatment groups.

Biofire Pneumonia Panel (BPP) in ATTACK, con't

- The Biofire FilmArray® 2.0 Pneumonia Panel (BPP) was used in ATTACK to enable early identification of ABC in respiratory samples from HABP/VABP patients being evaluated for enrollment eligibility
  - Nearly all activated sites were provided with the Biofire FilmArray 2.0 instrument and BPP pouches
  - Although the BPP test can detect multiple viral or bacterial pathogens, only positive results for *Acinetobacter* spp. were considered/documented for enrollment purposes in ATTACK

Bacteria

Acinetobacter calcoaceticus-baumannii complex
Enterobacter cloacae
Escherichia coli
Haemophilus influenzae
Klebsiella oxytoca
Klebsiella pneumoniae group
Klebsiella aerogenes
Moraxella catarrhalis
Proteus spp.
Pseudomonas aeruginosa
Serratia marcescens
Staphylococcus aureus
Streptococcus agalactiae
Streptococcus pneumoniae
Streptococcus pyogenes

Atypical Bacteria

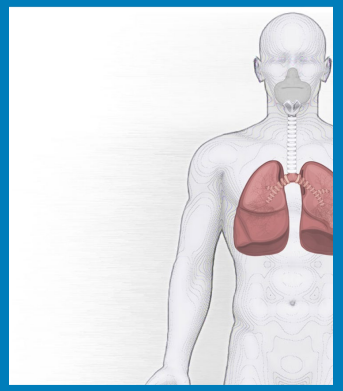
Chlamydia pneumoniae
Legionella pneumophila
Mycoplasma pneumoniae

Viruses

Adenovirus
Coronavirus
Human Rhinovirus/Enterovirus
Human Metapneumovirus
Influenza A
Influenza B
Parainfluenza virus
Respiratory Syncytial virus

Resistance Markers

mecA/C and MREJ
KPC
NDM
Oxa48-like
CTX-M
VIM
IMP



Chosen cutoff 10^5

HABP = hospital-acquired bacterial pneumonia, VABP = ventilator-associated bacterial pneumonia

Biofire Pneumonia Panel (BPP) in ATTACK, con't

- In addition to the BPP test, a patient was required to have a respiratory sample processed for standard culture by the local microbiology laboratory.
- Patients who met all other enrollment criteria were randomized based on a positive ABC result from the BPP test while awaiting culture results from the local laboratory.
- However, if a respiratory sample that tested positive for ABC by BPP was not culture-positive for ABC at the local microbiology laboratory, the patient was deemed ineligible for randomization and withdrawn from the trial.
- The study protocol did not require documentation of negative BPP results nor subsequent culture results for respiratory samples that tested negative for ABC by BPP.

Distribution and use of BPP in ATTACK

- Devices and pouches were provided to 83 sites in 17 countries
- 73.5% of sites used the provided Biofire BPP to evaluate pneumonia patients
- A total of 422 BPP tests were performed for ATTACK
- *Unlikely that each BPP test result corresponded to a single enrollment decision*

Distribution and use of BPP in ATTACK

Country	Sites that received BPP (N)	Sites that used BPP (N)	% of Sites that used BPP	Total BPP tests used (N)
China	18	17	94.4	155
Taiwan	4	4	100.0	108
Russia	9	8	88.9	43
Peru	5	4	80.0	30
Thailand	4	2	50.0	23
India	6	5	83.3	16
Belarus	4	3	75.0	11
Turkey	6	4	66.7	9
Mexico	4	2	50.0	7
Hungary	3	3	100.0	6
Greece	5	2	40.0	4
Lithuania	3	2	66.7	3
S. Korea	1	1	100.0	3
Brazil	5	2	40.0	2
Israel	3	1	33.3	1
USA	2	1	50.0	1
Puerto Rico	1	0	0	0
Total	83	61	73.5	422

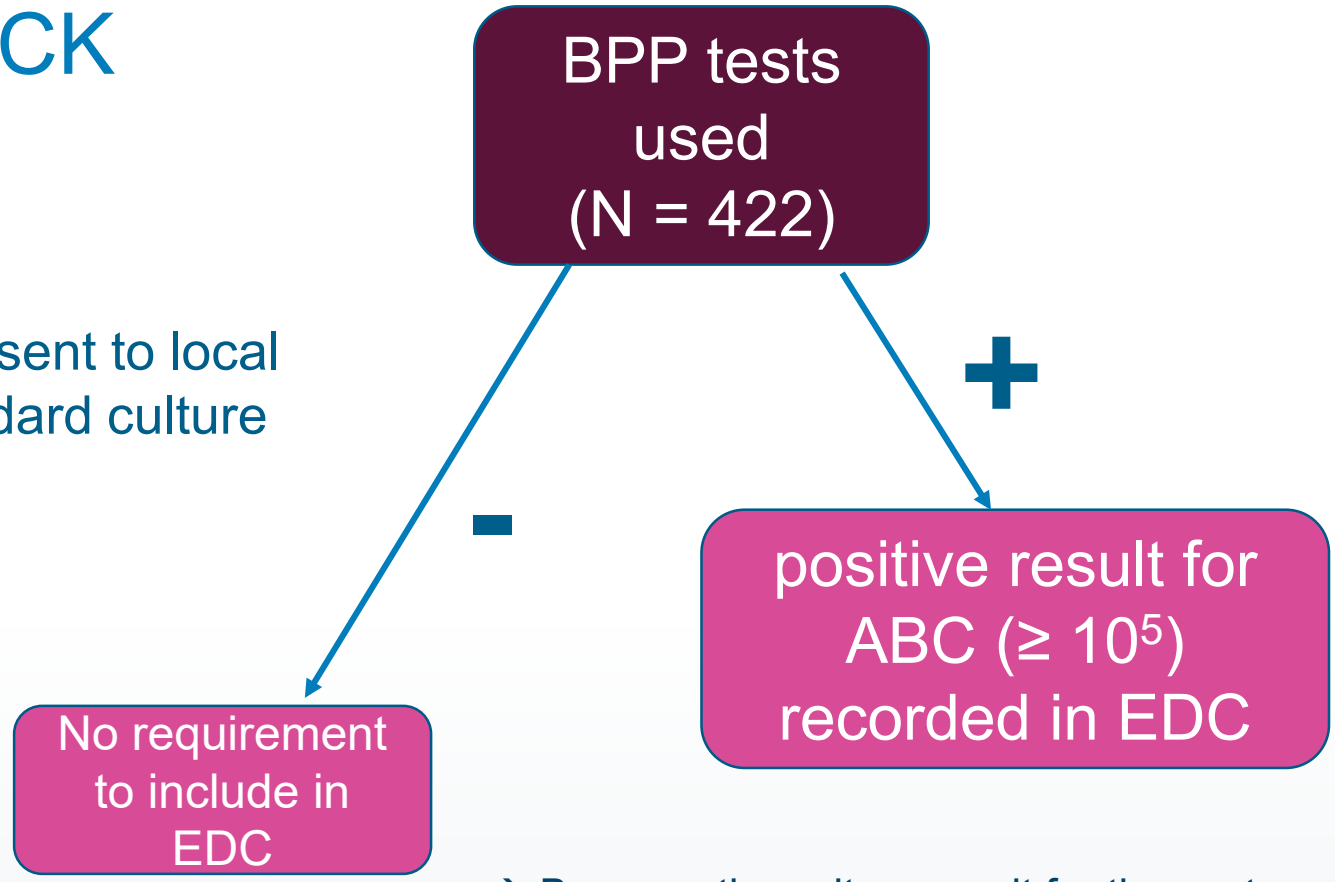
Performance of BPP in ATTACK

531 patients screened for enrollment

All samples were sent to local micro lab for standard culture

467 (88%) pneumonia (HABP, VABP)

64 (12%) bacteremia

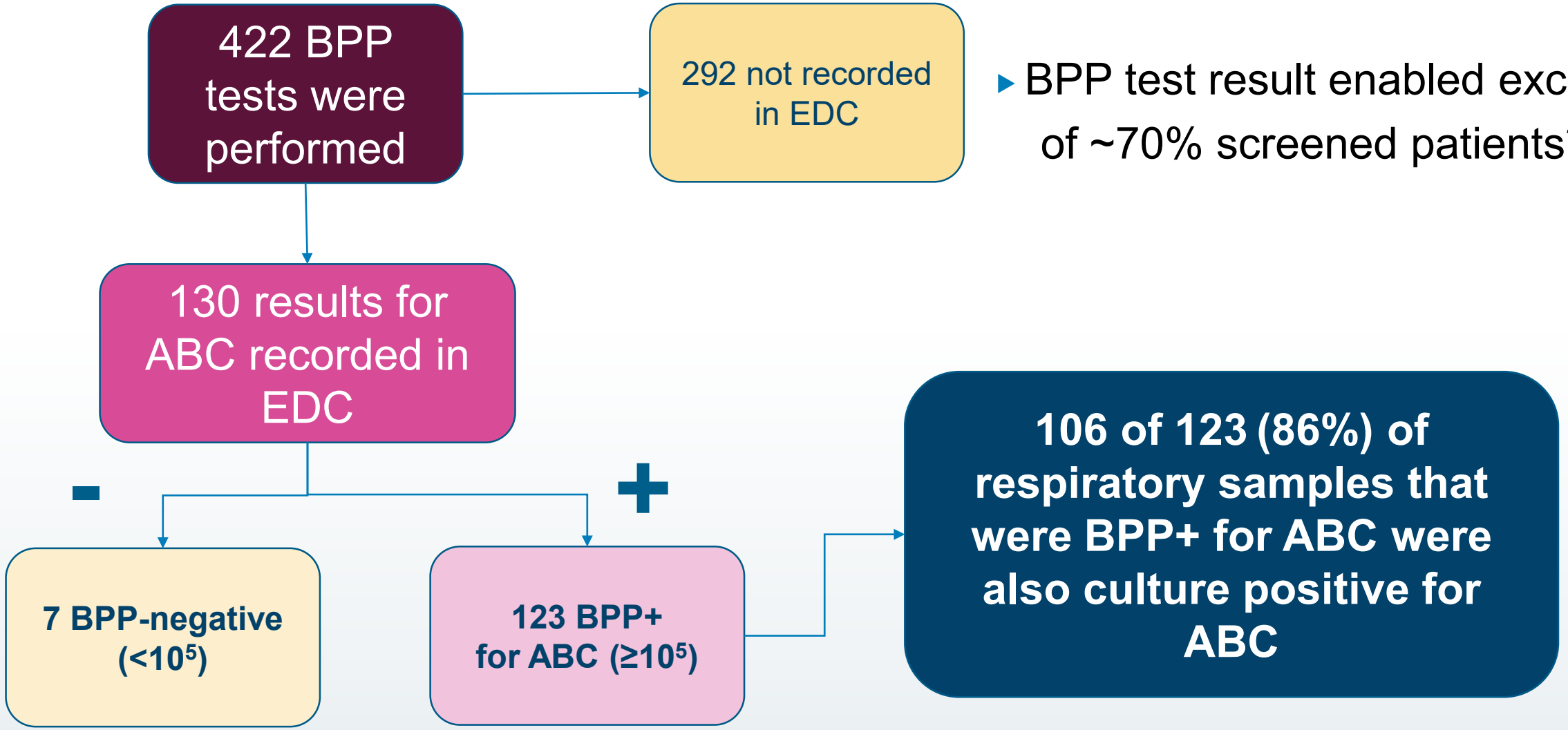


→ Because the culture result for the vast majority of samples that tested negative for ABC by BPP was not entered in the EDC, it was not possible to calculate the sensitivity and specificity of the BPP test for ABC in ATTACK

HABP = hospital-acquired bacterial pneumonia, VABP = ventilator-associated bacterial pneumonia

EDC = electronic data capture

Performance of BPP in ATTACK



- BPP test result enabled exclusion of ~70% screened patients*

*Unlikely that each BPP test result corresponded to a unique enrollment decision

Conclusions

- ATTACK represents the first successful completion of a clinical trial to evaluate pathogen-directed therapy for MDR Gram-negative infections
- A key component of this trial was inclusion of a rapid test to enable enrollment decisions within 48 hours

- Over 70% of sites provided with the test used it at least once
- The vast majority of pneumonia patients were evaluated by BPP

- ~70% of pneumonia patients screened were excluded from enrollment
- 86% of respiratory samples that were BPP^{+} for ABC were also culture-positive for ABC

Proof of Concept for Personalized Antibacterial Therapy

- Taken together, these data suggest enrollment of pathogen-directed clinical trials can greatly benefit from the use of a rapid diagnostic test.

- Results from ATTACK suggest this type of personalized antibacterial therapy can lead to better patient outcomes

ENTASIS THERAPEUTICS

BIOMÉRIEUX

PIONEERING DIAGNOSTICS