Strategies to Get the Dose Right for Phase III Clinical Trials: What is Required?

Shampa Das

Director of Clinical Pharmacology,
AstraZeneca, Macclesfield, UK
Email: shampadasPKPD@gmail.com

ASM Microbe 2017, New Orleans
3rd June, 2017

Disclosures

- Shampa Das is an employee of and shareholder in AstraZeneca
- The studies discussed in this presentation were sponsored by AstraZeneca and Allergan Inc. AstraZeneca's rights to ceftazidime-avibactam were acquired by Pfizer in December 2016
- Editorial support was provided by Risha Bulusu of Prime, Knutsford, UK, supported by AstraZeneca and Pfizer

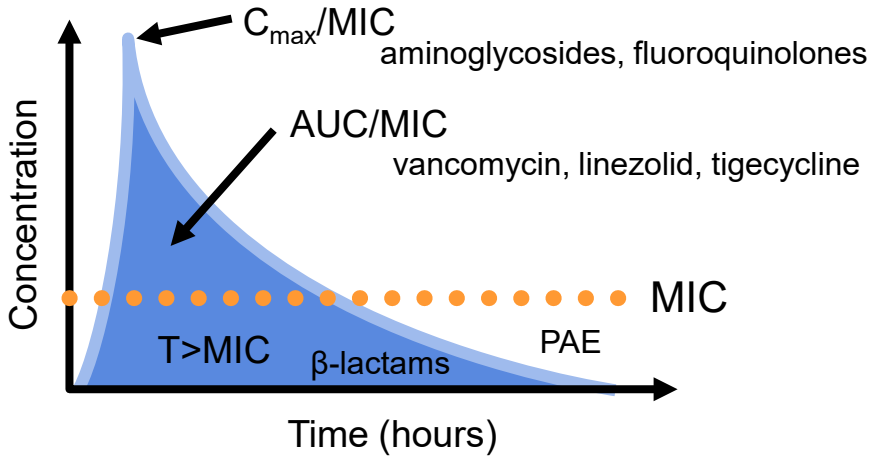
Introduction

- Sub-therapeutic PK exposure could not only lead to lack of efficacy but also emergence of resistance
- Understanding of PK/PD targets
  - What is the relationship between drug concentration and effect – i.e. what is the PK/PD driver?
  - What concentration of drug is required to achieve efficacy?
  - What MIC is it important to cover (is dose chosen to cover MIC_{90}?)
- In what compartments are drug concentrations required for efficacy?
  - Eg. plasma, specific tissue
- Understanding of PK of the drug and what affects PK
  - Eg. patient population (healthy volunteers vs patients), renal /hepatic impairment
- Understanding PK/PD makes it possible to optimize dose for special populations (eg. renal dysfunction)

Using PK/PD for Dose Selection in Antibacterial Drug Development

- Action of the drug is directly on bacteria so PK/PD targets considered to be robust and predictive

- Need to characterize the relationship between drug concentration and effect
  - i.e. understand the PK/PD driver
- Derive the magnitude of the PK/PD driver
  - This establishes the PD target (PDT)

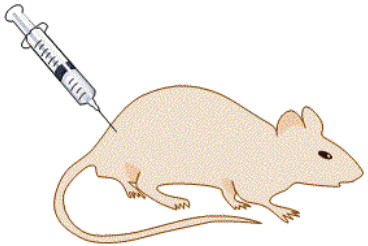


- Select a dose which will achieve the PDT in the **majority of patients**

How to Study the PK/PD Driver

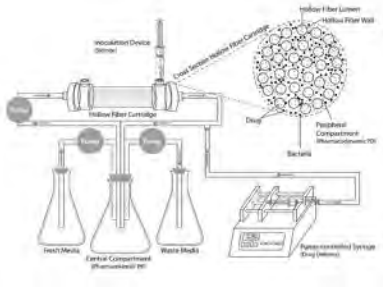
- Choose preclinical models most relevant for the indication

Mouse neutropenic thigh and lung models



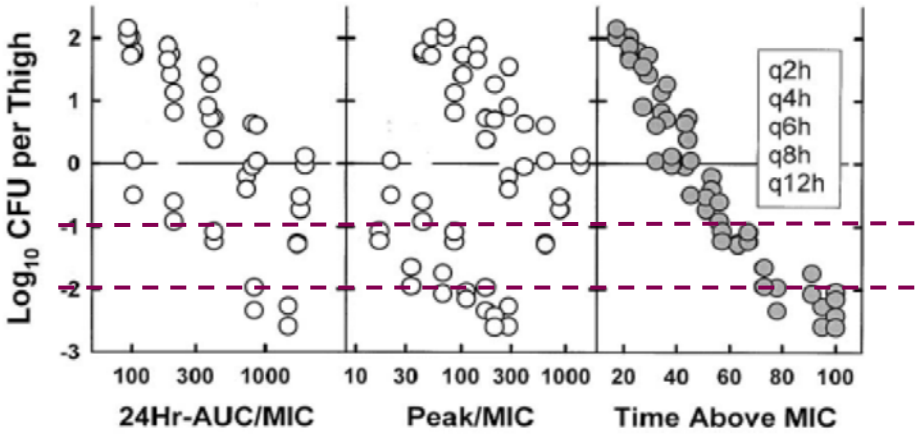
- Gold standard – useful to have some *in vivo* data
- Can relate efficacy to site of action

Hollow fiber



- Simulate human PK
- Easier to test different doses and dosing intervals, and longer durations
- Can test high innocula
- Higher turnaround – can test numerous organisms
- Can investigate emergence of resistance

Considerations for Evaluation of PDT



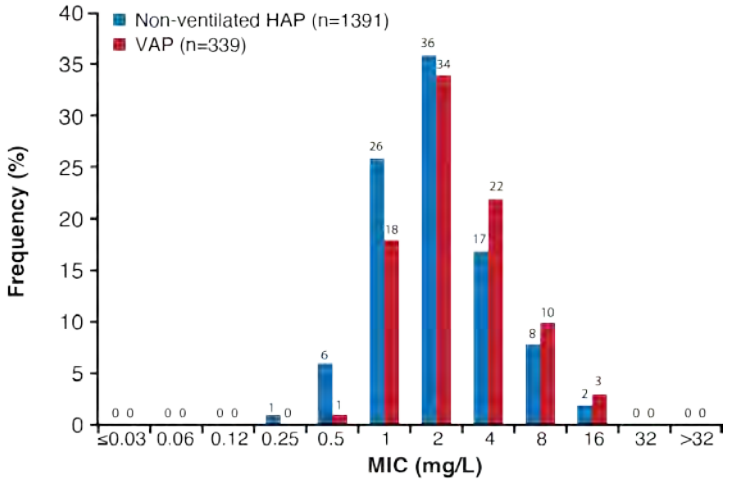
What target is most relevant for the indication (stasis, 1 or 2 log kill)?

- Does the choice of organisms used in evaluating the target represent clinical use?
  - Consider type and number, particularly if expect a small number of target pathogens in clinical trials

Craig WA. *Infec Dis Clin N Am.* 2003;17:479–501.

Target MIC

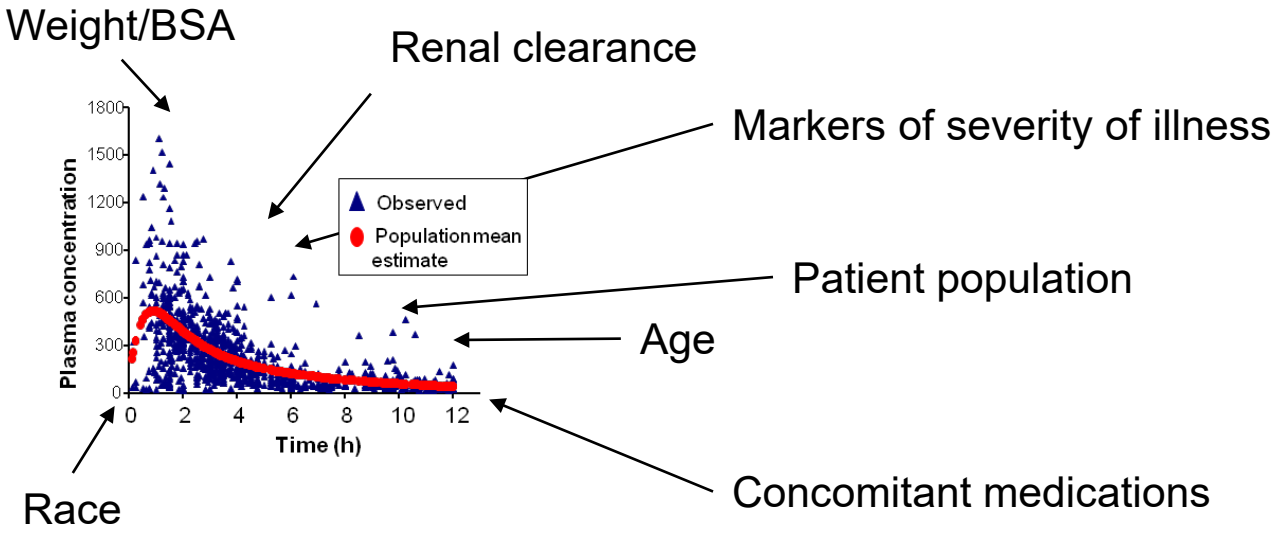
- What MIC is it important to cover?
  - Ideally want the dose to cover the majority of organisms that will be encountered
  - i.e. may want to cover MIC_{90}
  - Choose dose to cover least susceptible pathogen



- Has infection site been considered? Eg. bacterial isolates from NP are believed to represent a generally less susceptible group of isolates than those from other infections
- Does the PDT evaluation include isolates with MICs at the upper target range?

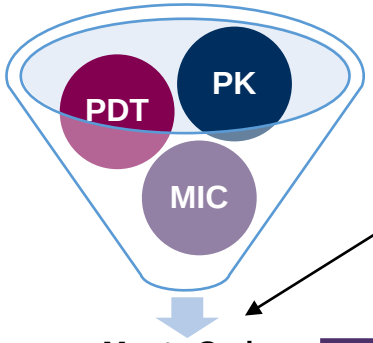
Das S et al. ECCMID 2015. Abstract P1289.

Population PK



Build a population PK model

How to Derive the Dose Using a PDT

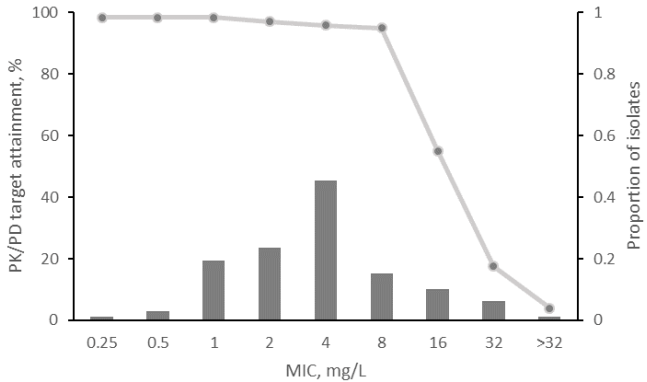


Monte Carlo Simulation (MCS)

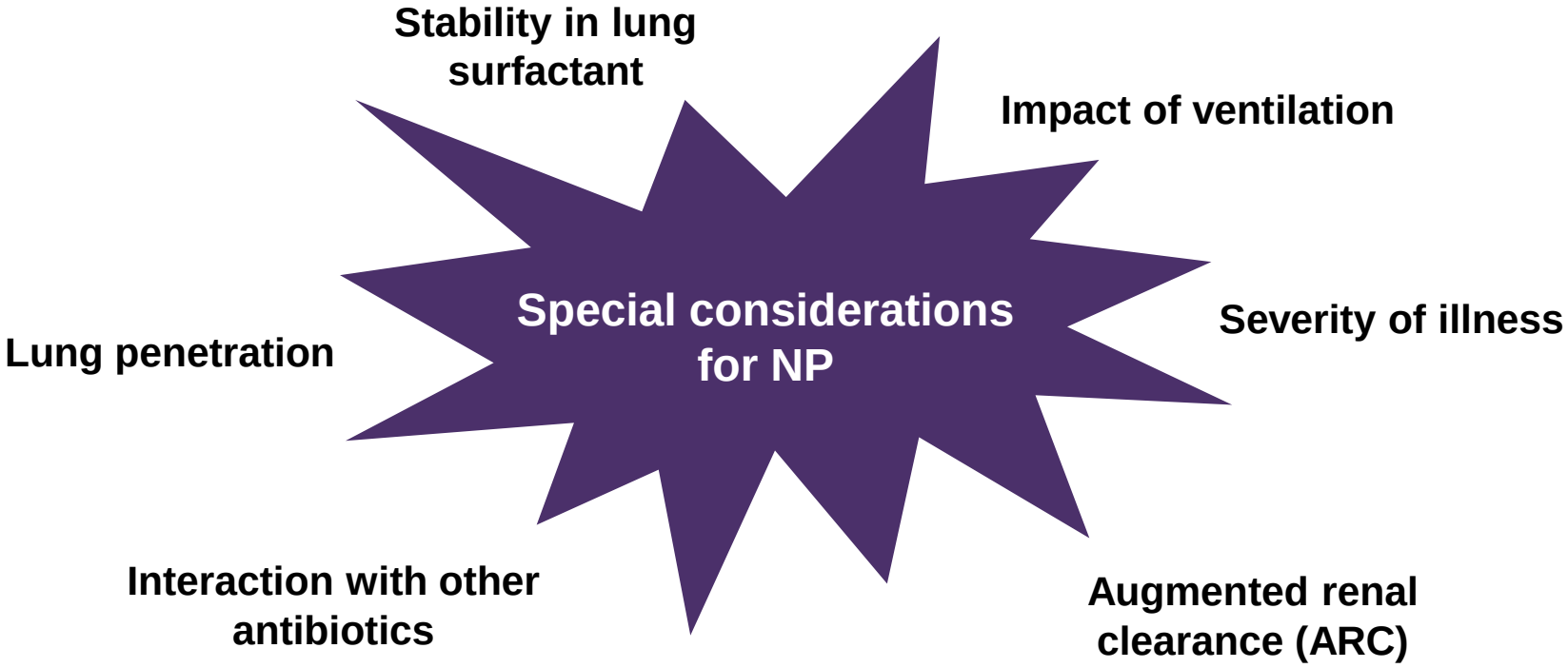
Using MCS you are simulating the variability seen in patients in greater numbers

Calculate probability of target attainment (PTA)

Choice of dose will be a balance between that which achieves sufficient PTA at a target MIC and is well tolerated



Selecting the Right Dose for Nosocomial Pneumonia (NP) is Challenging



Interaction with Pulmonary Surfactant

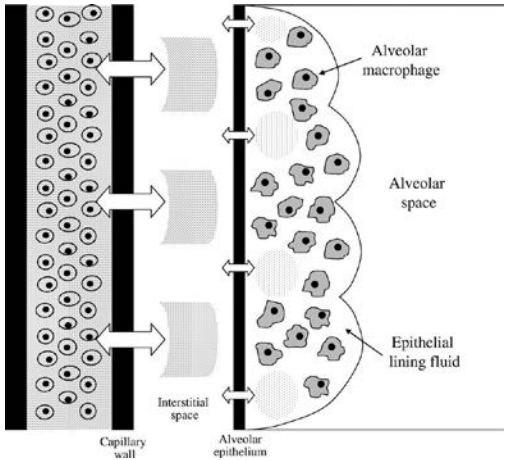
- Daptomycin is approved for use in complicated skin and skin structure infections but not pneumonia[1]
  - Non-inferiority was not achieved in a daptomycin Phase 3 community-acquired pneumonia trial[2]
  - Further investigation elucidated that interaction with pulmonary surfactant resulted in inhibition of antibacterial activity[3]
- Thus it is important to investigate stability in pulmonary surfactant

1. Cubicin. Prescribing information 2017. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021572s058lbl.pdf.
2. Pertel PE et al. *Clin Infect Dis*. 2008;46:1142–1151.
3. Silverman JA et al. *J Infect Dis*. 2005;191:2149–2152.

Lung Penetration

- Not accounting for drug concentrations at site of infection can lead to potential underdosing

Is plasma the right target?



Pulmonary epithelial lining fluid (ELF) is often used to represent lung penetration

- However, need to consider how the ELF data are used:
  - Are you looking for PTA in ELF? If so is the PDT in ELF the same as plasma
  - Are you validating plasma as a surrogate target?

Kiem S, Schentag JJ. *Antimicrob Agents Chemother*. 2008;52:24–36.

Disease State

- NP can be associated with high severity of disease
  - Consider whether this impacts PK and thus achieving therapeutic concentrations
- NP can be associated with augmented renal clearance (ARC)
  - For renally cleared drugs, this could result in underdosing (eg. doripenem and ceftobiprole)
- Potential impact of mechanical ventilation on PK also needs to be considered

Case Study of Dose Selection for Use of Ceftazidime-Avibactam (CAZ-AVI) to Treat NP (Including VAP)

- CAZ-AVI is a BL-BLI approved in the EU and US for the treatment of cIAI and cUTI[1,2]
- It is also approved for treatment of NP (including VAP) in the EU[2]
- Whilst CAZ-AVI was in development for treatment of cUTI and cIAI, additional work was undertaken to assess whether the same dose would be suitable for NP
- Initial EU approval was achieved in NP based on extrapolation of efficacy and exposure from cIAI and cUTI[2]

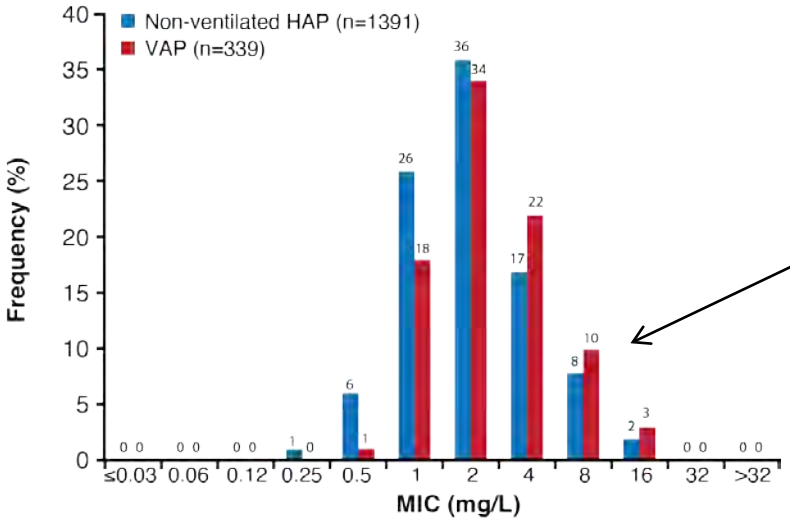
1. AVYCAZ prescribing information. 2017. Available from: https://www.allergan.com/assets/pdf/avycaz_pi.
2. Summary of Product Characteristics: Zavicefta. 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004027/WC500210234.pdf.

Steps Taken for CAZ-AVI Dose Selection for NP

1. Activity of CAZ-AVI assessed in the presence of lung surfactant
2. *In vitro* MIC interaction studies between CAZ-AVI and other antibacterial agents used in the treatment of NP
3. MIC target selection
4. Assessment of PK/PD driver and magnitude (lung infection model)
5. Assessment of relationship between plasma and ELF concentrations in healthy volunteers
6. Plasma PK characterized in healthy volunteers and patients and population PK models built
7. Joint PTA calculated with population PK model against the preclinical MIC target for CAZ and PD target for AVI
8. Dose which predicted >90% PTA selected

MIC Target Selection

- MIC target selection
  - MIC target assessed from panel of bacteria isolated as causative from patients with NP
  - Focus on *P. aeruginosa* data, the least-susceptible pathogen in the CAZ-AVI spectrum

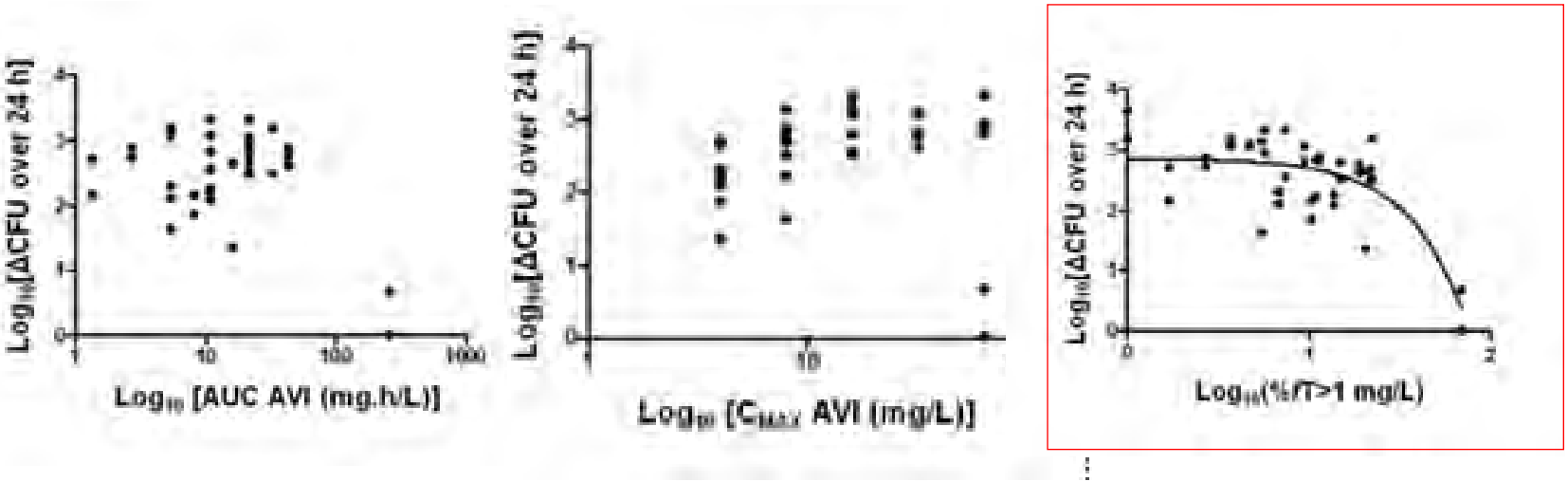


MIC target of 8 mg/L based on MIC_{90}

Das S et al. ECCMID 2015. Abstract P1289.

Assessment of PK/PD Driver and Magnitude

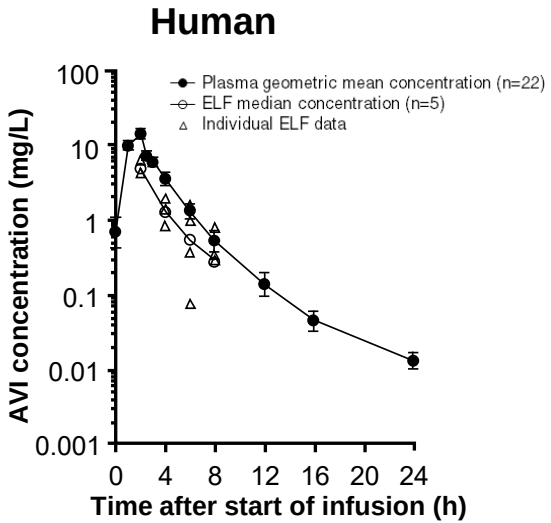
- Assessment of PK/PD driver and magnitude in mouse neutropenic thigh and lung models infected with *P. aeruginosa*
  - PK in plasma and ELF in mouse was well-characterized

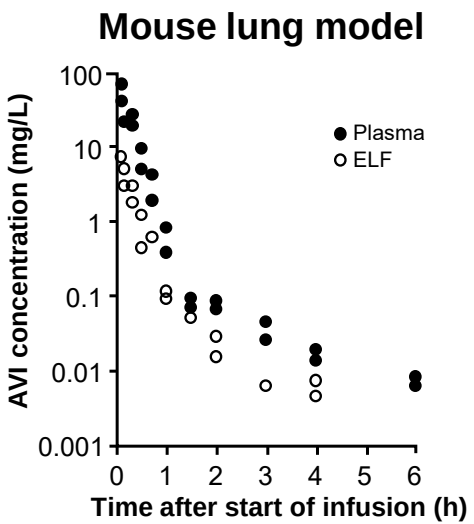


Berkhout J et al. *Antimicrob Agents Chemother*. 2015;60:368–375.

Validating Plasma as a Surrogate Target

- Relationship between plasma and epithelial lining fluid (ELF) explored in a Phase I clinical trial (NCT01395420)[1]
- Mouse and human plasma:ELF relationship compared[1–3]
- For ceftazidime and avibactam in both species ELF profile was similar to plasma, with higher penetration in humans, validating plasma as a surrogate[1–3]





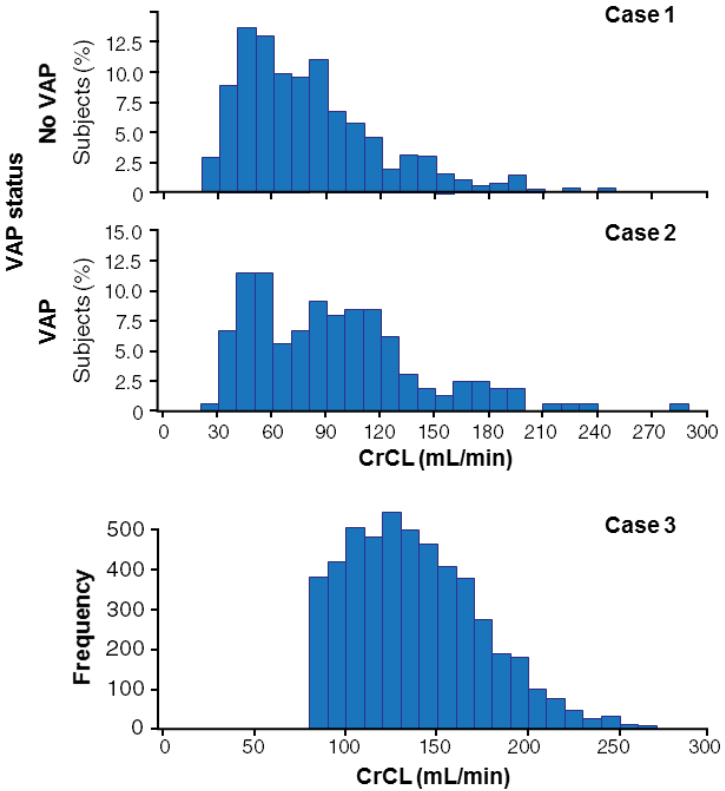
1. Nicolau D et al. *J Antimicrob Chemother*. 2015;70:2862–2869.
2. Berkhout J et al. *Antimicrob Agents Chemother*. 2015;59:2299–2304.
3. Das S et al. ECCMID 2015. Abstract P1288.

Probability of Target Attainment (PTA)

- Plasma PK/PD target for both CAZ and AVI defined, and used in joint PTA calculations
  - i.e. aim is to select a dose which is predicted to achieve the PK/PD targets in >90% of patients
- Plasma PK characterized in healthy volunteers and patients and population PK models built
  - Phase 2 data in cIAI patients were available at that time
- Literature data on CAZ allowed an assumption that PK in patients with NP would be comparable to patients with cIAI
- Joint PTA calculated with population PK model against the preclinical MIC target for CAZ and PD target for AVI

Li J et al. ECCMID 2015. Abstract P1289.

Considering CrCL Distribution in PTA Simulation



- The Phase 2 data allowed characterization of relationship of plasma exposure with CrCL
- High proportion of ARC identified in VAP population
- To test if dose was sufficient for patients with high CrCL different simulation scenarios were tested during the MCS
- The Phase 3 dose was predicted to achieve >90% PTA even in patients with high CrCL

Ambrose PG et al. *Clin Infect Dis* 2010. 51(S1):S103–S110.
Li J et al. ECCMID 2015. Abstract P1289.

Validation of Dose Selection

- Dose selected for the NP trial was the same dose used for cIAI and cUTI trials
- Non-inferiority to meropenem has now been demonstrated in a Phase 3 clinical trial in NP including VAP (REPROVE; NCT01808092)
- Positive Phase 3 data validate the dose and exposure associated with efficacy
- Understanding the PK/PD relationship allows assessment of whether the dose was sufficient for all patient subgroups

Torres A et al. ECCMID 2017. Abstract 2556.

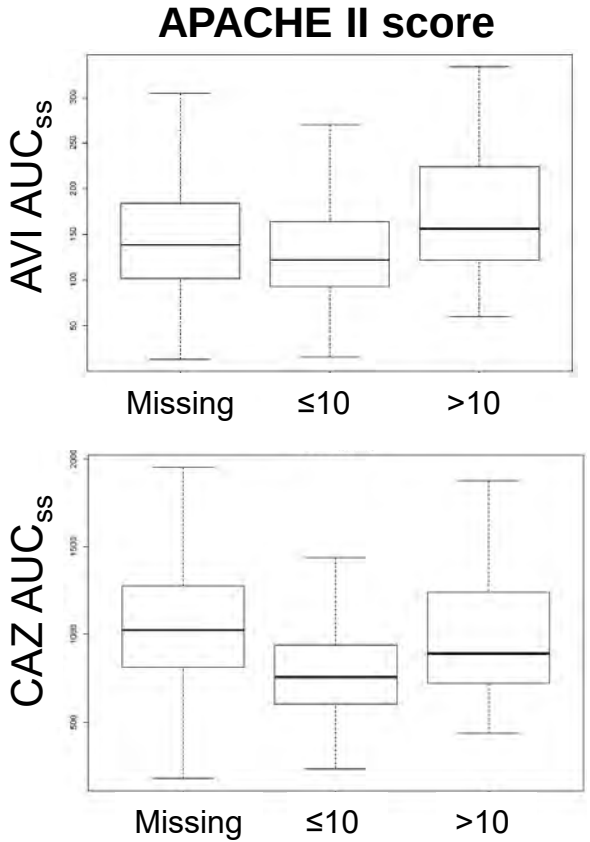
Importance of PK Sampling in Phase 3

- Population PK model
  - PK samples (sparse) taken from **ALL** Phase 3 patients
  - Final models comprise data from almost 1500 subjects; the **vast majority of whom were patients** with cUTI, cIAI or NP
  - Established the main influence of variability as CrCL, age and whether the subject is a patient or healthy volunteers

- Phase 3 population included patients with wide spread of:
  - CrCL
  - Disease state (eg. wide range of APACHE score, fever, WBC etc)
  - Age, weight, ethnicity
  - Co-medications

Das S et al. ECCMID 2017. Abstract 2628.

Assessment of Exposure by Disease Severity



- PK was compared in patients with high APACHE score (>10) vs ≤10
- Similar comparisons made for presence of SIRS, high WBC, bacteremia
- This allowed assessment of whether the dose of CAZ-AVI was adequate in patients with more severe illness
- Whilst for CAZ-AVI there was no impact on PK – by assessing and understanding PK/PD, if there was an effect you could dose adjust

Das S et al. ASM 2016. Abstract 500.

Using PK/PD to Dose Adjust

- Both CAZ and AVI are predominantly renally cleared[1,2]
- Exposure (AUC) and half-life increase with increasing renal impairment
- By understanding the PK/PD relationship can use joint PTA analysis to optimize dose adjustment (rather than just adjusting based on AUC)
- Dose adjustments were selected based on PTA and exposure predictions[3,4]
- A reasonable proportion of patients had high CrCL (>150 ml/min)
  - Whilst for CAZ-AVI slightly lower exposure was achieved, dose adjustment was not required as PTA was still >95% in these patients[4]
- Caution – renal function can improve rapidly in some patients!

1. Welage LS et al. *Antimicrob Agents Chemother*. 1984;25:201–204.
2. Merdjan H et al. *J Clin Pharmacol.* 2017;57:211–218.
3. Li J et al. AAPS 2015. Abstract 2459.
4. Das S et al. ECCMID 2017. Abstract 2628.

Conclusions

- To ensure robust dose selection for NP it is important to:
  - Understand the PK/PD relationship in an appropriate preclinical model, using representative organisms
  - Understand the impact of penetration into lung
  - Consider disease and patient related factors which could impact exposure
- With a good understanding of PK/PD relationship, and PK in the patient population, can ensure the right dose for all patient groups

Acknowledgements

AstraZeneca

- Wright Nichols
- Jianguo Li
- Paul Newell
- Diansong Zhou

Wright Dose Ltd

- James Wright
- Merran MacPherson