MGB Biopharma

# Bringing True Novelty to Anti-Infective Treatment

New Class of Antibacterials Based on
a Completely New Mechanism of Action

BioTrinity
London
11th-13th May 2015

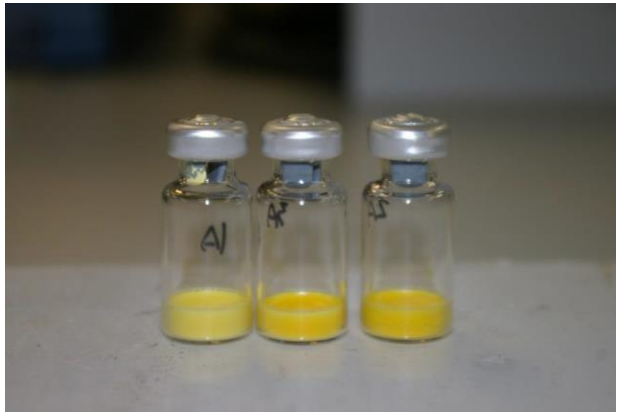
# MGB Biopharma – Delivering True Novelty

- Founded in April 2010 – HQ in Glasgow, Scotland - and funded by an Angel syndicate and the Scottish Co-Investment Fund
- Developing a truly novel class of drugs against infectious diseases based on the University of Strathclyde's DNA Minor Groove Binder (MGB) Platform Technology
- This platform provides an opportunity to develop various compounds against bacteria, viruses, fungi and parasites with a completely new mode of action which is distinct from the antimicrobial drugs used in clinical practice today
- **MGB-BP-3** is the first compound from this platform, with strong activity against Gram-positive pathogens. Currently in clinical phase I study

# MGB-BP-3
# IV formulation for systemic Gram-positive infections

# MGB-BP-3 intravenous formulation

- Under development for the treatment of hospital acquired systemic Gram-positive infections (susceptible and resistant *Staphylococcus, Streptococcus and Enterococcus*)
- MGB-BP-3 lyophilised as a succinic salt
- Reconstituted with WFI or 5% dextrose
- Manufacturing optimisation and up-scaling successfully completed



- Acute tolerability study in mouse confirmed MTD of 100mg/kg (anticipated human dose 7-15mg/kg)
- Pharmacokinetic profile supports bolus and continuous intravenous administration
- Good *in vivo* activity confirmed in mouse infection models
- ADME ongoing
- Nonclinical safety studies started

# MGB-BP-3 intravenous - Technical Batch

- Technical batch manufacture of a lyophilised product is complete
- Final formulation is 25mg/mL MGB-BP-3 in 25mg/mL mannitol/0.2 M succinic acid
- T=1M stability data available shortly
- No issues or concerns with any preliminary data so far
- Lyophilised product is ready for use in Project 2 – *in vivo* POC models

# Human Plasma Compatibility Study

| Test formulation | Replicated samples | Observation 1 (immediately after addition to plasma) | Observation 2 (30 minutes after addition to plasma) | Formulation pH | Plasma/formulation mixture pH (immediately after addition to plasma) | Plasma/formulation mixture pH (30 minutes after addition to plasma) |
|---|---|---|---|---|---|---|
| Negative control | 1 | C | C | NM | NM | NM |
| | 2 | C | C | | | |
| Positive control | 1 | LT | T | NM | NM | NM |
| | 2 | LT | T | | | |
| MGB-BP-3 25 mg/mL formulation | 1 | SJ | SJ | 3.19 | 3.89 | 3.92 |
| | 2 | SJ | SJ | | | |
| MGB-BP-3 12.5 mg/mL formulation | 1 | LJ | LJ | 3.38 | 4.27 | 4.30 |
| | 2 | LJ | LJ | | | |
| MGB-BP-3 6.25 mg/mL formulation | 1 | T | T | 3.24 | 4.74 | 4.77 |
| | 2 | T | T | | | |
| MGB-BP-3 3.13 mg/mL formulation | 1 | T | T | 3.34 | 5.40 | 5.56 |
| | 2 | T | T | | | |
| MGB-BP-3 1.56 mg/mL formulation | 1 | LT | T + F | 3.40 | 6.16 | 6.45 |
| | 2 | LT | T + F | | | |
| MGB-BP-3 1.17 mg/mL formulation | 1 | LT | LT | NM | NM | NM |
| | 2 | LT | LT | | | |
| MGB-BP-3 1.00 mg/mL formulation | 1 | LT | LT | NM | NM | NM |
| | 2 | LT | LT | | | |
| MGB-BP-3 0.78 mg/mL formulation | 1 | C | C | 3.51 | 6.57 | 6.61 |
| | 2 | C | C | | | |
| MGB-BP-3 0.39 mg/mL formulation | 1 | C | C | 3.46 | 6.90 | 7.12 |
| | 2 | C | C | | | |
| MGB-BP-3 0.19 mg/mL formulation | 1 | C | C | 3.49 | 7.05 | 7.28 |
| | 2 | C | C | | | |

C : clear, limpid and transparent
F : flocculation
LJ : dense liquid jellification
LT : light turbidity
NM : not measured
SJ : solid jellification
T : turbid

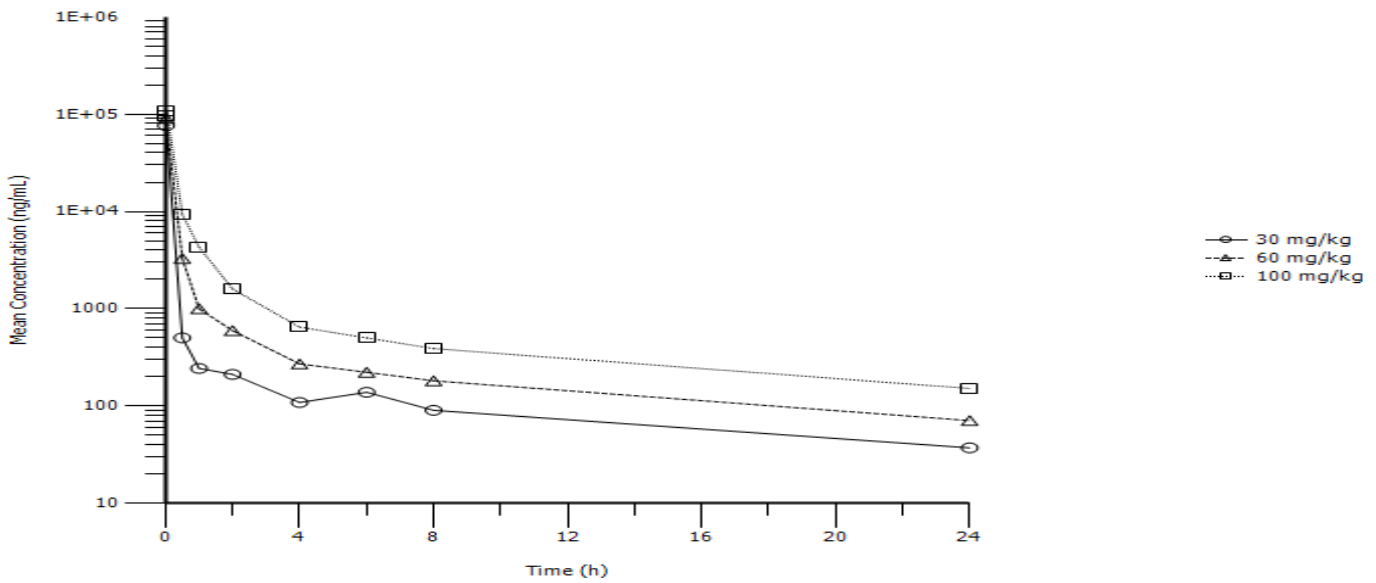
# Intravenous Set Compatibility Study

- Syringes (Polyethylene, 10mL & 30mL, supplied by HMR London)
  - There was no significant change to the appearance or pH at ambient, 2-8°C or controlled ambient
  - After 8 hours storage recovery was ≥100%
  - No significant increase to the total number of related substances at any of the storage conditions
  - **25 mg/mL MGB-BP-3 is considered stable when stored in syringes for up to 8 hours at ambient, controlled ambient and 2 - 8°C**
- Infusion Bags (Ethyl vinyl acetate, supplied by HMR London)
  - No significant change to the appearance or pH after 24 hours storage at ambient conditions, exposed to light
  - After 24 hours storage at ambient conditions recovery of 101% was recorded.
  - No significant increase to the total number of related substances was recorded after 24 hours storage at ambient conditions
  - **5 mg/mL MGB-BP-3 in 5% dextrose is stable when stored in infusion bags at ambient conditions for up to 24 hours**
- Infusion Lines (polyethylene clear and amber, supplied by HMR London)
  - There was no loss of active material for either tubing type with all assay results comparable (98.0 - 102.0%) to that of the bulk solution
  - There was no change in purity profile for either tubing type

# Pharmacokinetic Profile of MGB-BP-3

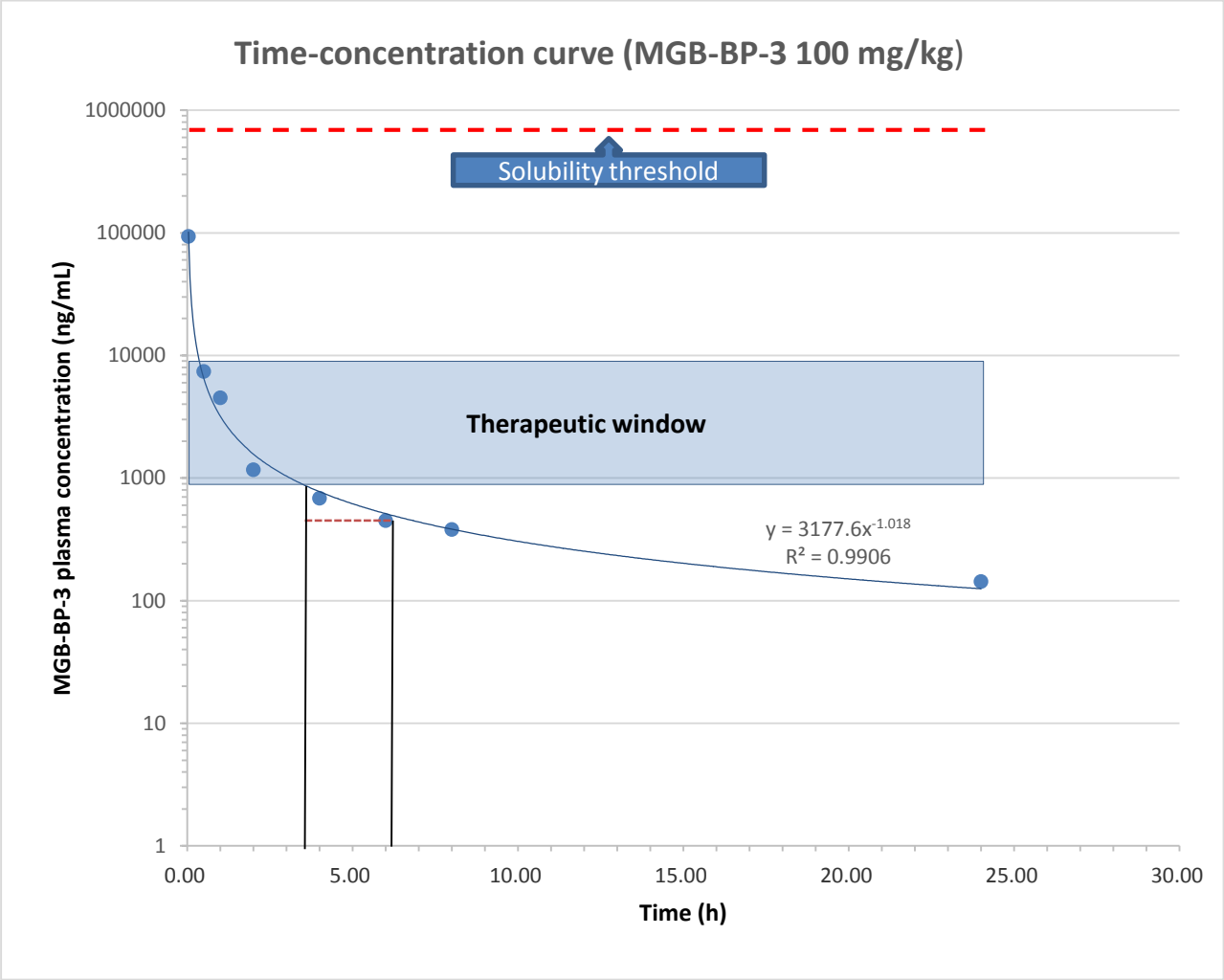
# PK – tolerability mouse study

Mice were dosed at: 30mg/kg, 60mg/kg and 100mg/kg.
- 30mg/kg and 60mg/kg were tolerated when administered over a 2 minute period
- 100mg/kg was tolerated when administered over a 3 minute period



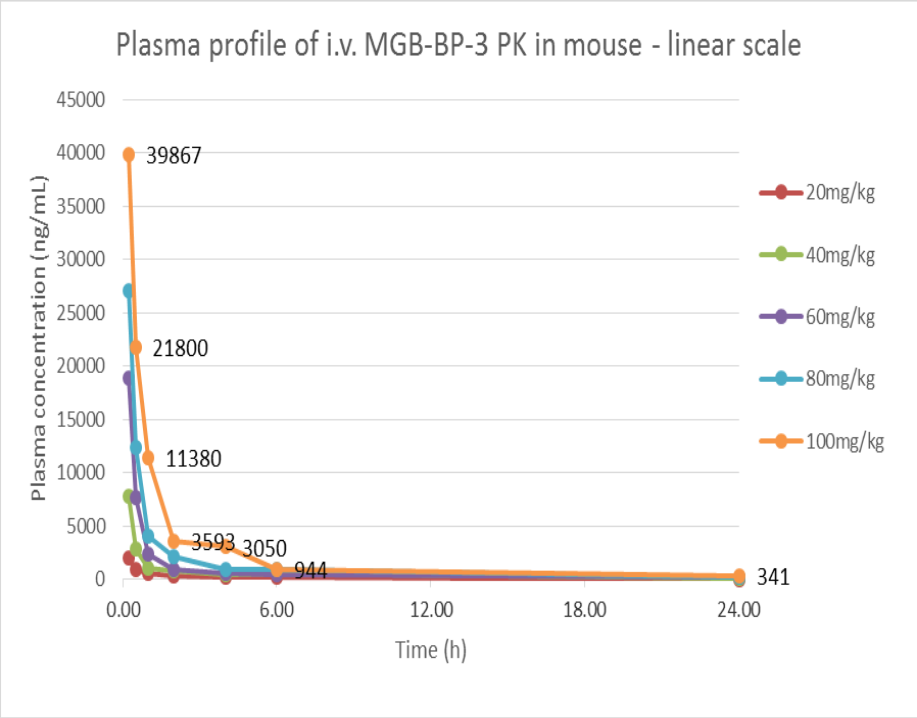

| Group | Dose (mg/kg) | $C_{max}$ (ng/mL) | $t_{max}$ (h) | $AUC_{0-t}$ (h*ng/mL) | $AUC_{0-\infty}$ (h*ng/mL) | $AUC_{ex}$ (%) | $t_{1/2}$ (h) | CL (mL/min/kg) | Vz (mL/kg) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 30 | 76300 | 0.017 | 22200 | 22700 | 2.5 | 10 | 22.0 | 19900 |
| 2 | 60 | 90400 | 0.017 | 29900 | 31100 | 3.7 | 11 | 32.2 | 31300 |
| 3 | 100 | 110000 | 0.033 | 46100 | 48400 | 4.9 | 11 | 34.4 | 32400 |

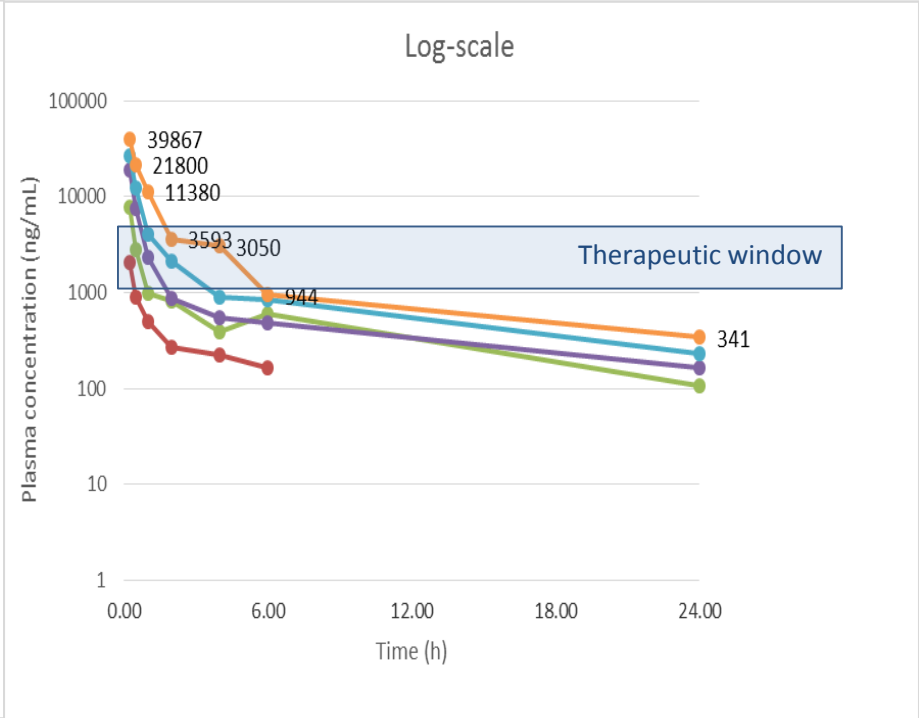
# PK Mouse Study



# PK profile in mouse

- Time-concentration profiles of five single MGB-BP-3 doses administered intravenously over 1 minute were assessed in mouse.
- No mortality was observed. The highest doses provoked some discomfort in the animals, which was prevented on predosing with paracetamol.
- This PK profile was used for the PK/PD modelling

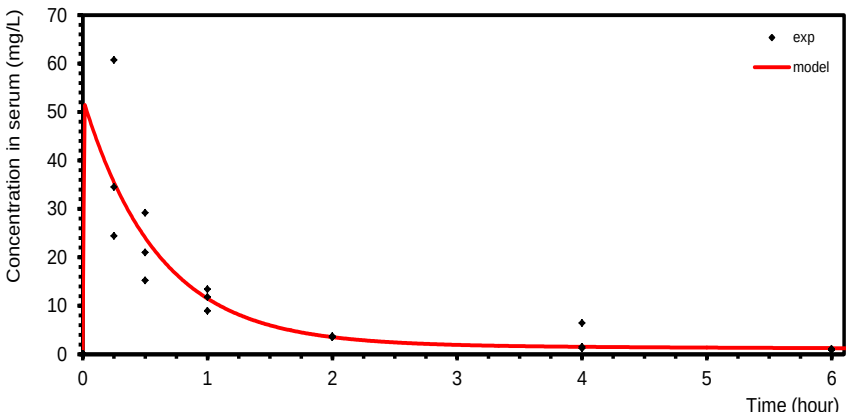


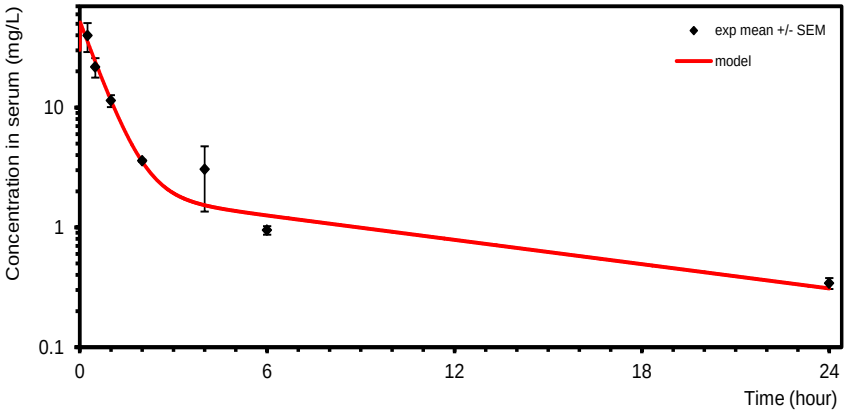



# Mouse PK profile – compartmental analysis

Compartment model fit of conc-time data for 100 mg/kg dose (total conc) with i.v. injection time T = 1.0 minute.

Compartmental analysis showed that MGB-BP-3 fits a two-compartment model with a fast distribution phase and slow elimination phase.



# MGB-BP-3 - Assessment of *in vivo* activity

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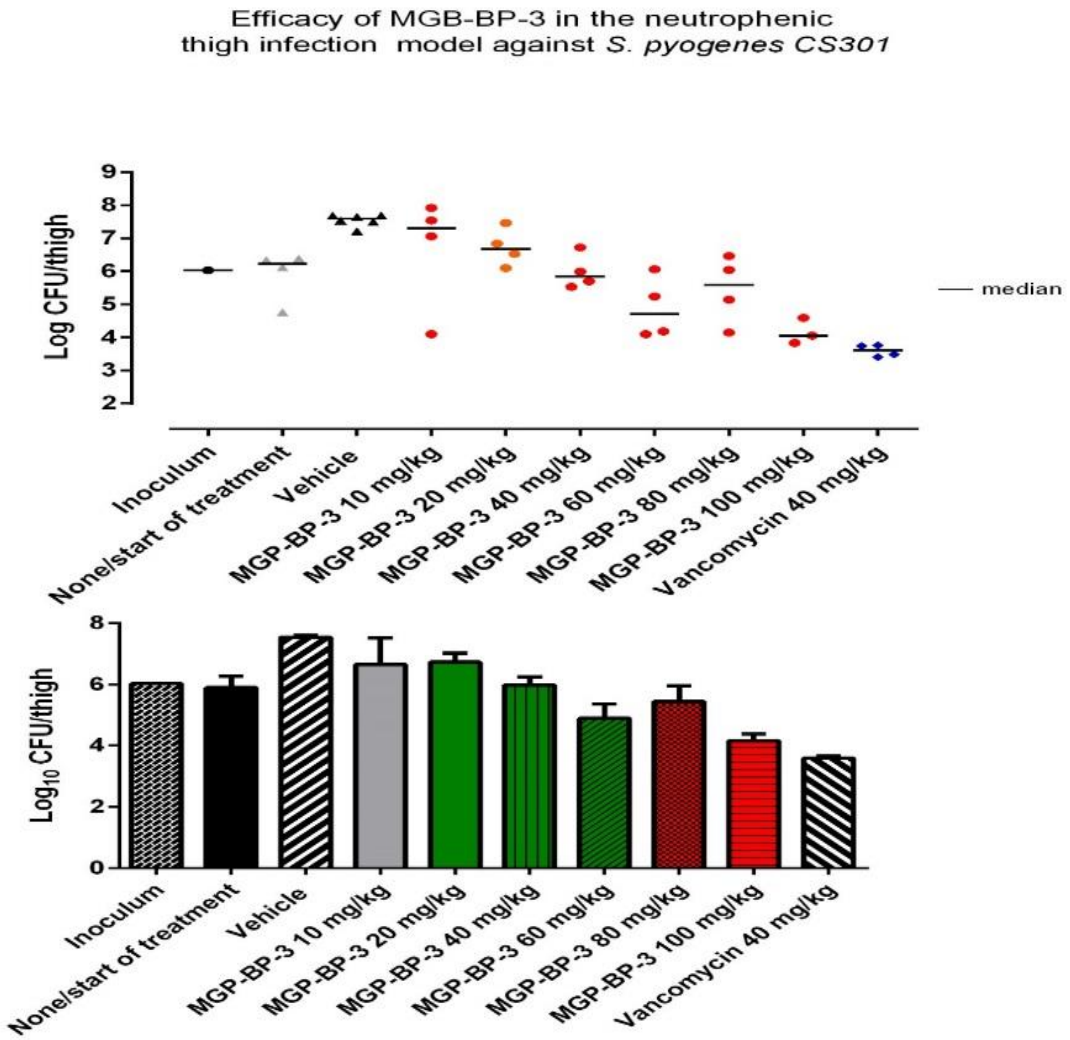
**The following studies were performed in order to profile MGB-BP-3 in vivo activity:**

1. **Assessment of MIC for the tested pathogens**
2. **Single dose mouse thigh model with:**
   - *Streptococcus pyogenes*
   - *Streptococcus pneumoniae*
   - *Staphylococcus aureus* (MRSA)
3. **Fractionated dose mouse thigh model with:**
   - *Streptococcus pneumoniae*
   - *Staphylococcus aureus* (MRSA)
4. **Mathematical PK/PD modelling**
5. **Efficacy assessment in mouse pneumonia model with:**
   - *Streptococcus pneumoniae*

# Activity of single MGB-BP-3 doses against *S. pyogenes* in the thigh mouse model

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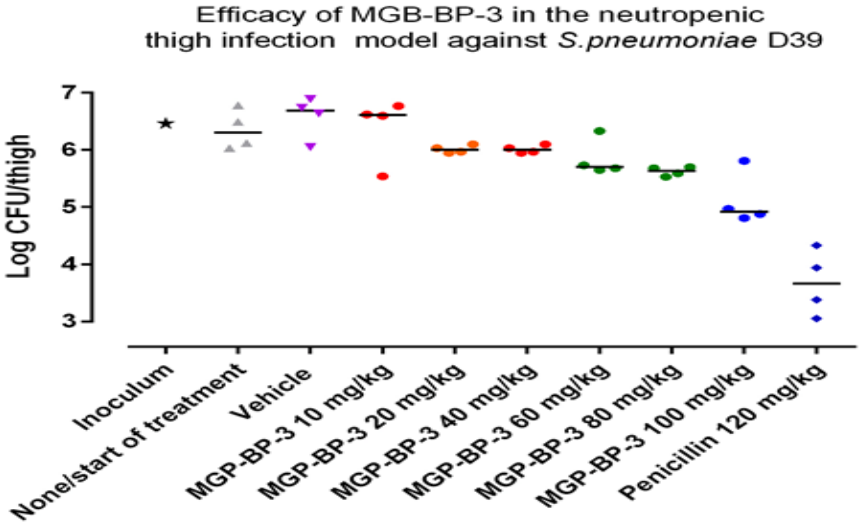
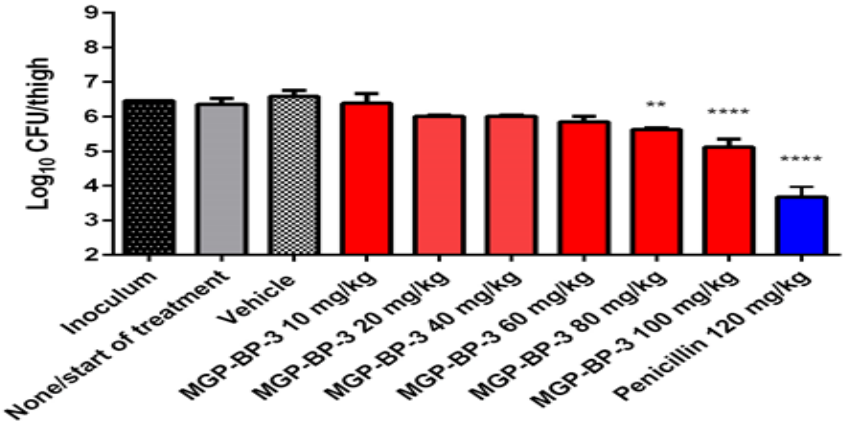
# Activity of single MGB-BP-3 doses against *S. pneumoniae* in the thigh mouse model

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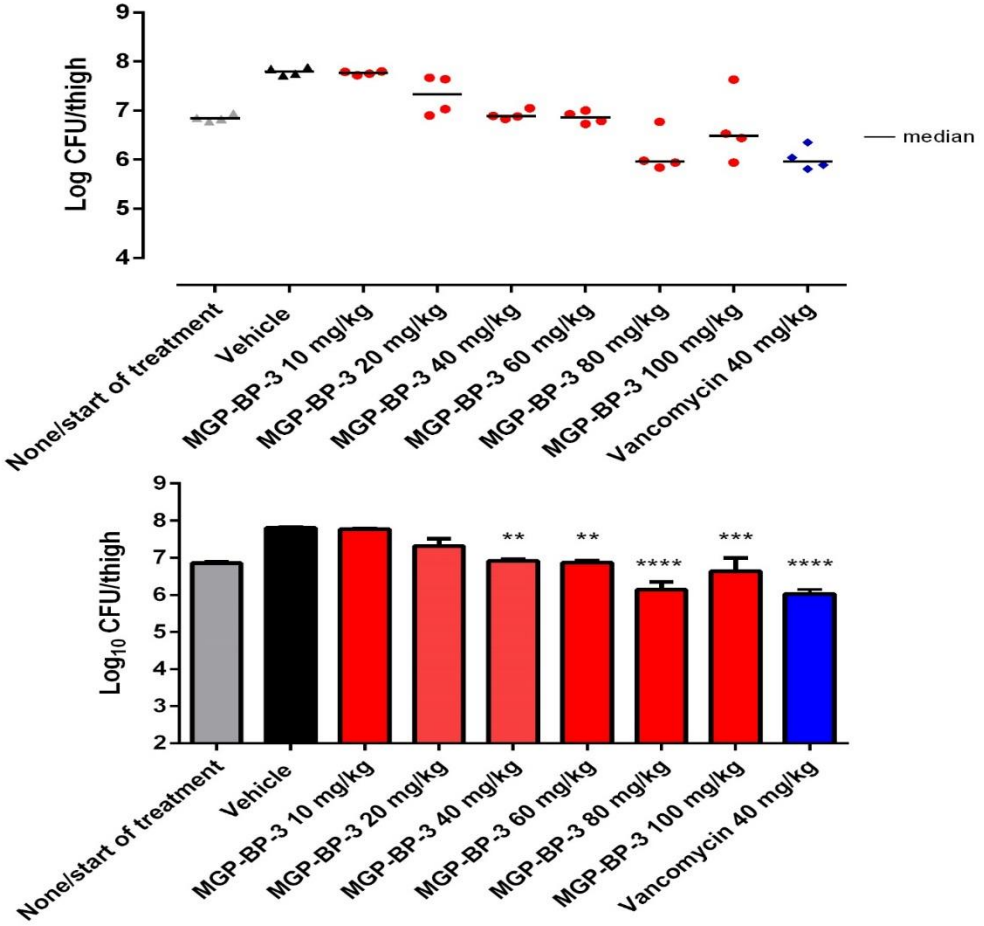
# Activity of single MGB-BP-3 doses against MRSA in the thigh mouse model

Efficacy of MGB-BP-3 in the thigh infection model against *S. aureus MRSA43484*

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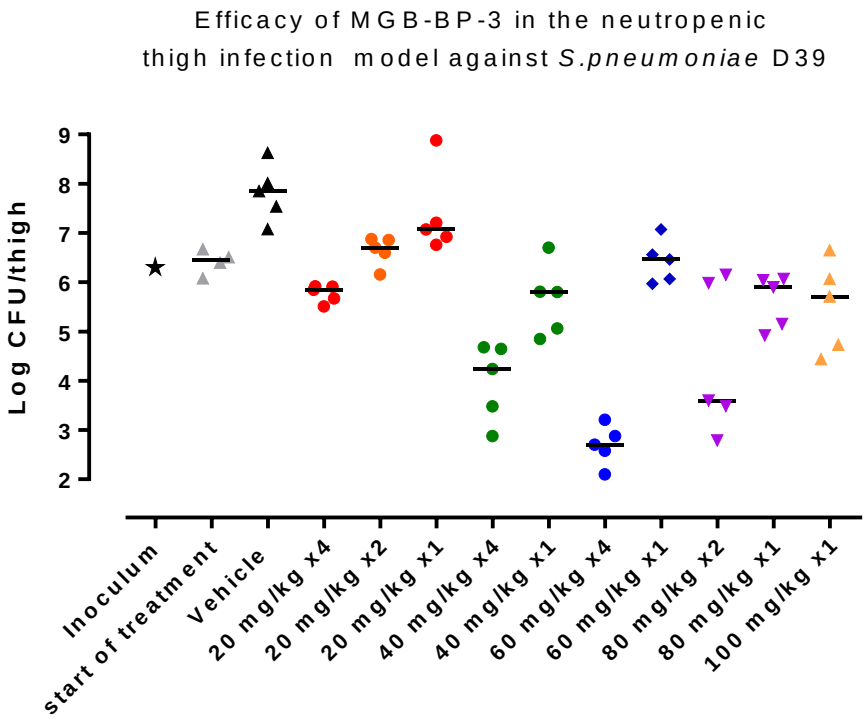
# Project 2

## MGB-BP-3 in mouse thigh infection fractionated dosing model with *S. pneumoniae*

MGB-BP-3 against *S.pneumoniae* was investigated following i.v administration of single and multiple dosing ranging from 20 - 100 mg/kg. The colony counts in the thighs were determined at 24 hrs after start of treatment.

| | Dosing (h) | | | |
|---|---|---|---|---|
| **MGB-BP-3** | **T=1** | **T=7** | **T=13** | **T=19** |
| None | x | | | |
| Vehicle | x | x | | x |
| 20 mg/kg | x | x | x | x |
| 20 mg/kg | x | | x | |
| 20 mg/kg | x | | | |
| 40 mg/kg | x | x | x | x |
| 40 mg/kg | x | | | |
| 60 mg/kg | x | x | x | x |
| 60 mg/kg | x | | | |
| 80 mg/kg | x | | x | |
| 80 mg/kg | x | | | |
| 100 mg/kg | x | | | |

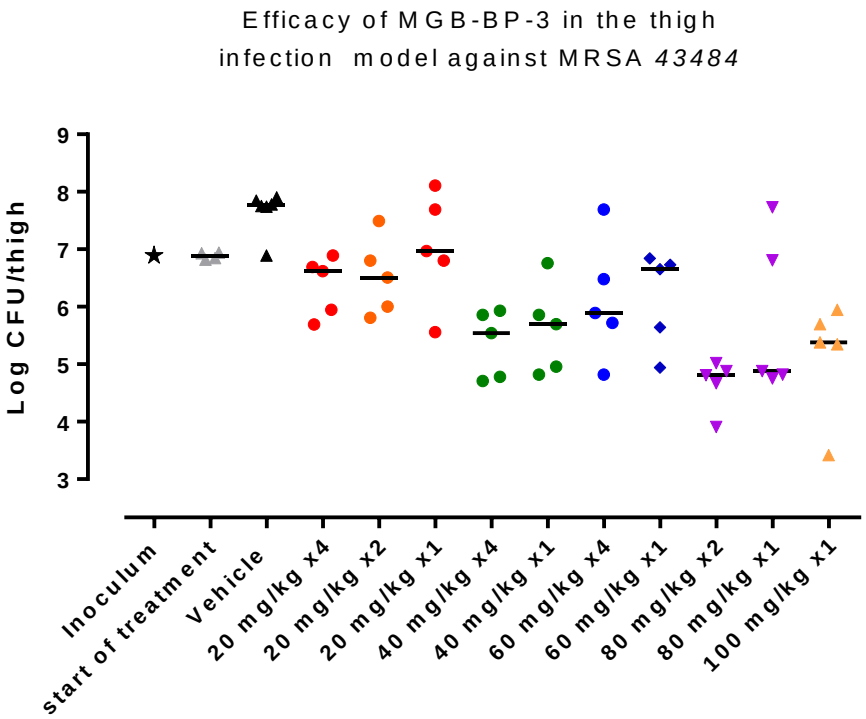


# Project 2

# MGB-BP-3 in mouse thigh infection fractionated dosing model with *MRSA*

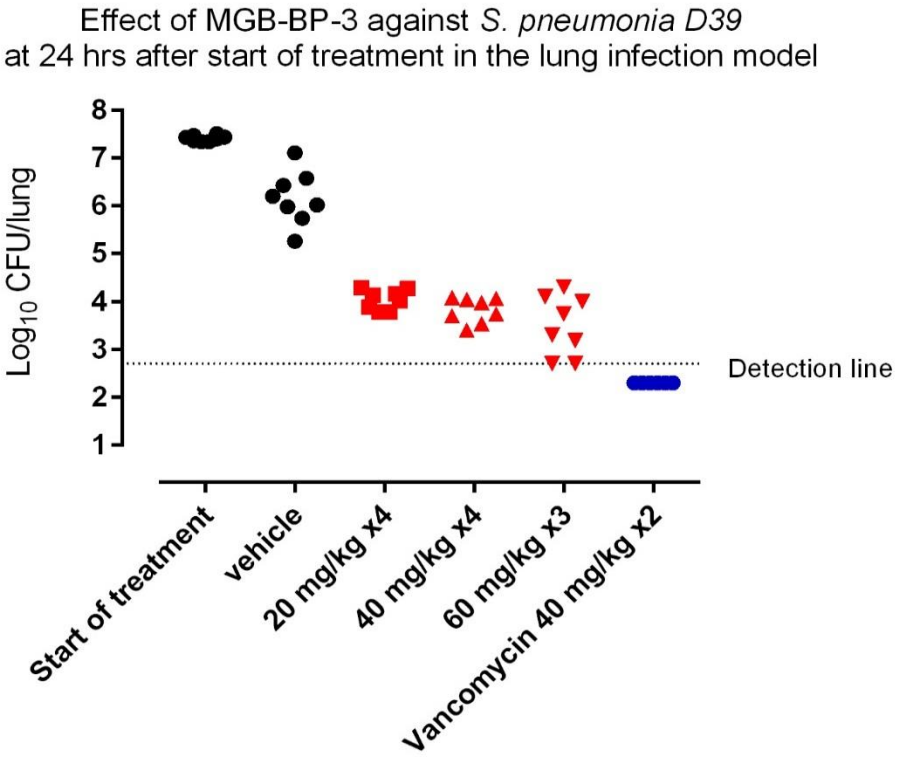
MGB-BP-3 against *MRSA* was investigated following i.v administration of single and multiple dosing ranging from 20 - 100 mg/kg. The colony counts in the thighs were determined at 24 hrs after start of treatment.

| | Dosing (h) | | | |
|---|---|---|---|---|
| **MGB-BP-3** | **T=1** | **T=7** | **T=13** | **T=19** |
| None | x | | | |
| Vehicle | x | x | | x |
| 20 mg/kg | x | x | x | x |
| 20 mg/kg | x | | x | |
| 20 mg/kg | x | | | |
| 40 mg/kg | x | x | x | x |
| 40 mg/kg | x | | | |
| 60 mg/kg | x | x | x | x |
| 60 mg/kg | x | | | |
| 80 mg/kg | x | | x | |
| 80 mg/kg | x | | | |
| 100 mg/kg | x | | | |



# Project 2
# MGB-BP-3 in mouse pneumonia infection disease model with *S. pneumoniae*

- Mice were inoculated intranasally and treatment initiated 4h after inoculation.
- Mice were treated intravenously with MGB-BP-3, vehicle or vancomycin as a positive control.
- MGB-BP-3 was dosed at 20mg/kg x4, 40mg/kg x 4 and 60mg/kg x3. Vancomycin was dosed at 40mg/kg x2.
- All mice were monitored for clinical signs of toxicity and discomfort and euthanized if severe symptoms persisted for more than 30 minutes.
- Lungs were collected at 24 hr after inoculation. CFUs were determined and the ED50 calculated.



# MGB-BP-3
# Full Clinical Development Plan

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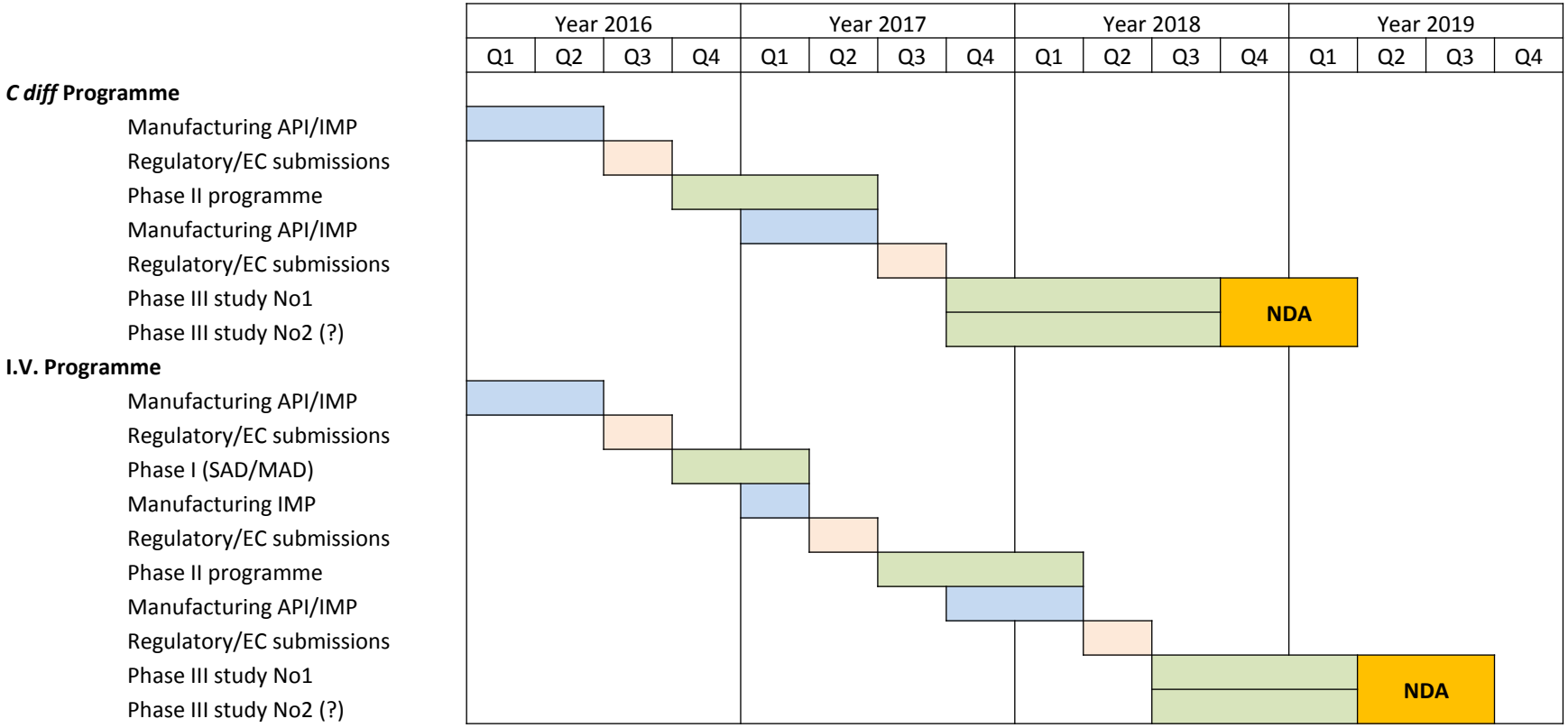


# MGB-BP-3 Cost of full clinical development

| **Oral C diff:** | |
|---|---|
| Regulatory and misc: | £ 100,000 |
| API/IMP Phase II | £ 500,000 |
| Phase II PoC (60 patients) | £ 2,500,000 |
| Total PoC | **£ 3,100,000** |
| Phase III (500pts) | £ 15,000,000 |
| Total to NDA | **£ 18,100,000** |

| **Intravenous** | |
|---|---|
| API/IMP Phase I: | £ 500,000 |
| Phase I SAD | £ 500,000 |
| Phase I MAD | £ 500,000 |
| IMP Phase IIa: | £ 200,000 |
| Phase II PoC (60 patients) | £ 2,500,000 |
| Total i.v. PoC | **£ 4,200,000** |
| Phase III (500pts) | £ 15,000,000 |
| Total to NDA | **£ 19,200,000** |

| **G&A for 3.5 years** | |
|---|---|
| Salaries | £ 2,016,536 |
| Consultancy | £ 60,000 |
| Patent fees | £ 205,000 |
| General Travel | £ 100,000 |
| Accountancy | £ 75,000 |
| UoS milestones | £ 220,000 |
| Facilities cost | £ 40,000 |
| General Insurance | £ 25,000 |
| Monitoring fees | £ 150,000 |
| Total to NDA | **£ 2,891,536** |
| Total to PoC (2.5 years) | **£ 2,250,000** |

Total to PoC for *C diff* and IV: £ 9,550,000

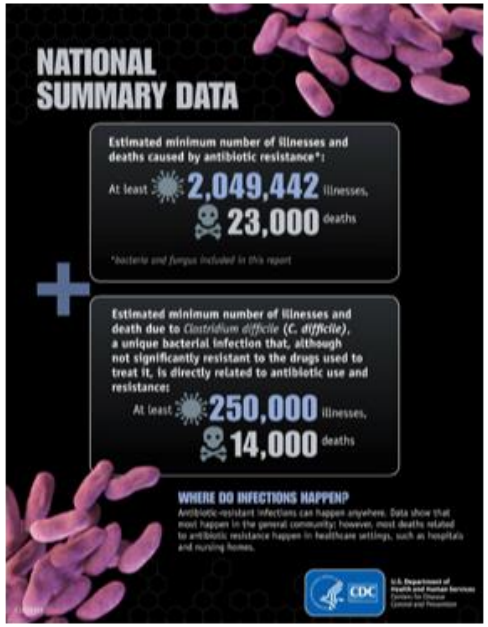
Total to NDA for *C diff* and IV: £ 40,000,000

# MGB-BP-3
# Business Aspect

# US Hospital Drug-resistant Infections

| Pathogen | Cases | Deaths |
|---|---|---|
| **Urgent Threats** | | |
| CRE | 9,300 | 610 |
| *N. gonorrhoea* | 246,000 | 5 |
| *C. difficile** | 250,000 | 14,000 |
| **Serious Threats** | | |
| MRSA | 80,000 | 11,000 |
| *S. pneumoniae* | 1,200,000 | 7,000 |
| VRE | 20,000 | 1,300 |
| *Pseudomonas* | 6,700 | 440 |
| *Campylobacter* | 310,000 | 28 |
| *Salmonella* | 100,000 | 40 |
| *Acinetobacter* | 7,300 | 500 |

*Estimated excess costs/year
$1,000,000,000




http://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf

# Competitor Products (1)

a) *Clostridium difficile*

| Product | Company | Stage | Class |
|---|---|---|---|
| SMT19969 | Summit | Ph 2 | novel |
| Cadazolid | Actelion | Ph 3 | Quinolonyl-oxazolidinone |
| Ramoplanin | Nanotherapeutics | Ph 2 | Lipoglycopeptide |
| Surotomycin | Cubist-Merck | Ph 3 | Lipopeptide |

**Source: PEW Charitable Trust December 2014**

# Competitor Products (2)

| Product | Stage | Company | Class | Gram -ve activity | Indication |
|---|---|---|---|---|---|
| Oritavancin | Approved Aug '14 | The Medicines Co | Glycopeptide | | absssi (MRSA) |
| Ceftolozane + Tazobactam | Approved Dec '14 | Cubist/Merck | cephalosporin + β-lactamase inhibitor | y | cuti, ciai, kidney |
| Dalbavancin (Dalvance) | Approved May' 14 | Actavis (Durata) | Lipoglycopeptide | | absssi; potential indications: cabp |
| Tedizolid (Sivextro) | Approved June' 14 | Cubist/Merck | Oxazolidinone | | abssi; potential indications: habp/vabp |
| Ceftolozane+Tazobactam (Zerbaxa) | Approved Dec '14 | Cubist/Merck | Novel cephalosporin+β-lactamase inhibitor | y | cuti, ciai, kidney; potential indications: habp/vabp |
| Oritavancin (Orbactiv) | Approved Aug '14 | The Medicines Company | Glycopeptide | | absssi caused by Gram-positive bacteria, including MRSA |
| Ceftazidime+Avibactam (CAZ-AVI) | Approved Feb ’15* | AZ/Actavis | Cephalosporin + novel β-lactamase inhibitor | y | cuti,ciai,kidney, habp/vabp |

* Approved on phase II data

# Competitor Products (3)

| Product | Stage | Company | Class | Gram -ve activity | Indication |
|---|---|---|---|---|---|
| Taksta (Fusidic acid)[9] | 3 | Cempra Inc. | Fusidane | | Prosthetic joint infections, absssi |
| Carbavance (RPX709+meropenem) | 3 | The Medicines Co | Meropenem + novel boronic β-lactam inh. | y | cuti, ciai, habp, vabp, neutropenia, bacteremia, kidney (CRE) |
| Delafloxacin | 3 | Melinta | Fluoroquinolone | y | absssi, cabp, gonorrhea,cuti, ciai |
| Eravacycline | 3 | Tetraphase | Tetracycline | y | ciai, cuti, habp |
| Plazomicin | 3 | Achaogen | Aminoglycoside | y | Bacteraemia, habp, vabp, ciai, cuti (CRE) |
| Solithromycin | 3 | Cempra Inc. | Macrolide (fluroketolide) | y | cabp, gonorrhea, urethritis |
| Finafloxacin | 2 | MerLion | Fluoroquinolone | y | cuti, kidney, acuteiai, sssi |
| POL7080 (RG7929) | 2 | Polyphor (Roche licensee) | Macrocycle (protein epitope mimetic) | y | vabp (pseudomonas), respiratory tract infection, bronchiectasis |
| AZD0914 | 2 | AstraZeneca | DNA gyrase inhibitor | y | Uncomplicated gonorrhea |
| S-649266 | 2 | Shionogi | Cephalosporin | y | Complicated uti |
| Debio 1452 | 2 | Debiopharm | Fabl inhibitor | | absssi (staphylococcal-specific) |
| Avarofloxacin | 2 | Actavis (formerly Furiex | Fluoroquinolone | y | cabp, absssi |
| Brilacidin | 2 | Cellceutix | Defensin-mimetic | | absssi |
| Ceftaroline+Avibactam | 2 | AZ/Actavis | Cephalosporin + novel β-lactam inh. | y | Bacterial infections[6] |
| CG-400549 | 2 | CrystalGenomics | Fabl inhibitor | | absssi |
| GSK2140944 | 2 | GlaxoSmithKline | T2 topoisomerase inhibitor | y | Respiratory tract infections, absssi, urogenital gonorrhea |
| Lefamulin (BC-3781) | 2 | Nabriva | Pleuromutilin | y | absssi, cabp, habp, vabp |
| Imipenem/cilastatin+relebactam (MK-7655) | 2 | Merck | Carbapenem + novel β--lactamase inhibitor | y | cuti, kidney, ciai, habp, vabp |
| Nemonoxacin[8] | 2 | TaiGen | Quinolone | y | cabp, diabetic foot, **absssi** |
| Omadacycline | 2 | Paratek | Tetracycline | y | cabp, absssi, cuti |
| Radezolid | 2 | Melinta | Oxazolidinone | y | absssi, cabp |
| Zabofloxacin | 2 | Dong Wha | Fluoroquinolone | y | Community-acquired bacterial pneumonia |

# Corporate Transactions

| Date | Acquiror | Target | Transaction | Stage | Up-front ($m) | Milestones ($m) |
|---|---|---|---|---|---|---|
| Dec '14 | Merck | Cubist | Acquisition | Market | 9500 | |
| Oct '14 | Actavis | Durata | Acquisition | Market | 675 | 150 |
| Feb '14 | Actavis | Forest | Acquisition | Market | 28000 | |
| Jul '13 | Cubist | Trius | Acquisition | 3 | 707 | 100 |
| Jul '13 | Cubist | Optimer | Acquisition | Market | 535 | 250 |
| | | | | | | |
| Nov '13 | Roche | Polyphor | Licence | 2 | 40 | 520 |
| Jan '15 | Roche | Meiji Seika/Fedora | Licence | 1 | n/d | 750 |
| Feb '14 | Roche | Discuva | Licence | Discovery | 16 | 175/drug |
| | | | | | | |
| Apr '15 | Nabriva | Vivo, Orbimed, etc | VC round | 3 | 120 | |
| Mar '15 | Red-X | | AIM IPO | pre-clinical | 22.5 | |

# The Market Opportunity

Global market for Antibiotics forecast to reach >$40 billion by the year 2015, propelled by intensive research in new areas of treatment, favourable regulatory environment and emergence of new drug classes.

USA is the single largest market for antibiotics followed by Europe and Asia-Pacific (driven by India and China which are forecasted to expand at the overall highest compounded growth rate through 2015).

The sales potential for the parenteral MGB BP-3 is substantial if as expected it is at least as effective as Pfizer's ZYVOX (linezolid). Pfizer reported ZYVOX revenues of over $1.18 billion in 2010. Cases of resistant bacterial strains have already emerged, and it is anticipated that full resistance might occur within the next few years.

The *Clostridium difficile* market has increased dramatically with over 350,000 cases reported in the USA in 2008. There is an alarming increase in resistant cases particularly in the elderly and the current standard treatments (vancomycin and metronidazole) are becoming less effective due to resistance. DIFICID (fidaxomicin) launched recently by Optimer in the USA has been estimated at peak sales of $500M in a recent independent analyst report.

# Where does MGB fit in?

Infectious Diseases Society of America's (IDSA) statement concerning fiscal year 2012 funding at the department of Health and Human Services, the Centers for Disease Control and Prevention, and National Institutes of Health Submitted to the House Appropriations Subcommittee on Labour, Health and Human Services, Education and Related Agencies April 15, 2011:

***"The antibiotic pipeline is bare particularly for drugs needed to address antibiotic-resistant bacteria. Collectively, highly problematic antibiotic-resistant organisms are summarized by the ESKAPE mnemonic: Enterococcus, Staphylococcus, Klebsiella, Acinetobacter, Pseudomonas, and ESBL (Enterobacter and E. coli). These bacteria have developed defenses that permit them to escape the actions of available antibiotics. The ESKAPE pathogens are currently the most important causes of the antibiotic resistance crisis in the US and other developed countries."***

***2 out of 7 pathogens listed in the ESKAPE are sensitive to MGB-BP-3***

# Generating Antibiotic Incentives Now (GAIN) Act

FDA issued a proposed rule listing pathogens that would be eligible for drug development incentives under the Generating Antibiotic Incentives Now (GAIN) Act. The pathogens are: species of *Acinetobacter, Aspergillus, Campylobacter, Candida,* ***Enterococcus*** *and Pseudomonas* as well as ***Clostridium difficile****, Enterobacteriaceae, Neisseria gonorrhoeae,* ***Neisseria meningitidis, Staphylococcus aureus, Streptococcus agalactiae, Streptococcus pneumoniae, Streptococcus pyogenes****, Vibrio cholerae,* the *Burkholderia cepacia* complex of species, the *Mycobacterium tuberculosis* complex of species and non-tuberculous *Mycobacteria* species. FDA is required to consider four factors in establishing and maintaining the list: impact on the public health due to drug-resistant organisms in humans, rate of growth of drug-resistant organisms, increase in resistance rates, and morbidity and mortality.

***7 out of 17 pathogens listed in the GAIN Act are sensitive to MGB-BP-3***

# Gram-positive Competitor Landscape

***Selected programmes including next generation iterations of existing classes and monoclonal antibodies / vaccines***

***New***

- *Affinium's AFN-1252, FAB-I inhibitor , oral Phase II, i.v. Phase I  Staph Aureus only activity*
- *Achillion's ACH 702, anti-MRSA and VRSA, late preclinical (MoA reported as targeting DNA replication enzymes)*

***"Next Generation":***

- *Paratek's Omadacyline (Aminomethylcycline – Heavily modified tetracycline) Phase III*
- *Forest's Avibactam "NXL-104" in combination with both ceftaroline and ceftazidime, Phase III*
- *Tetraphase TP834 Phase pre-IND*
- *Basilea's Ceftibiprole pre-registration*
- *Nabriva's BC-3781 Pleuromutilin – new class with already known MoA, Phase II (NB: also effective vs M Catarrhalis and H Influenzae :Gram –ve)*
- *Rib-X's Delafloxacin – quinolone with activity vs Gram pos and neg – Phase III*
- *Trius's TR-701, tedizolid, oxazolidinone Gram positive targeting MRSA, licensed to Bayer for emerging mkts, Phase III,*
- *Rib-X's radezolid, new generation oxazolidinone, Late Phase II*
- *Durata's dalbavancin, lipoglycopeptide Gram positive, long pk once a week i.v. in Phase III*

***Old:***

- *Cempra's sodium fusidate i.v formulation for MRSA*

***Biologics:***

- *Sanofi F598 antibody licensed from Alopexx , anti-MRSA and Y pestis (Phase I)*
- *Merck's V710 anti-MRSA vaccine (originator: Intercell) Phase II/III trial terminated mid 2011*

# MGB Biopharma Assets and positioning

1. *C diff* oral programme, clinical Phase I stage, with differentiation to *C diff* therapy
2. Gram +ve intravenous programme - successful intravenous formulation developed with high activity in animal infection models
3. Gram-ve, anti-viral and anti-parasitic as a part of the platform value

## MGB-BP-3 Positioning in the Market:

- A first choice medication for the treatment of *C. difficile* infections, especially caused by NAP1/027 strain.
- A novel intravenous anti-Gram positive agent to be used in line with the Antibiotic Stewardship policy where existing agents (such as vancomycin, daptomycin and linezolid) are relatively ineffective due to resistance.

MGB Biopharma

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