# Antimicrobial Pipeline and Drug Development

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**Topics:**

- Background
- The present situation
- Drugs recently approved and in late development
- Future issues
- Conclusions

Background:

Not enough new antibacterials or companies active in the therapeutic area

**FDA Approvals of new antibacterials 1983-2015 (Boucher et al, 2013, updated FDA website)**

| Years | Antibacterial approved |
|---|---|
| 1983-1987 | 16 |
| 1988-1992 | 14 |
| 1993-1997 | 10 |
| 1998-2002 | 6 |
| 2003-2007 | 5 |
| 2008-2012 | 2 |
| 2013-2015 | 6 |

(ceftazidime+avibactam; dalbavancin; oritavancin; tedizolid; telavancin; Ceftolozane+tazobactam)

## Active corporate antibacterial programmes: 1940 - onwards (Kinch et al, 2014)

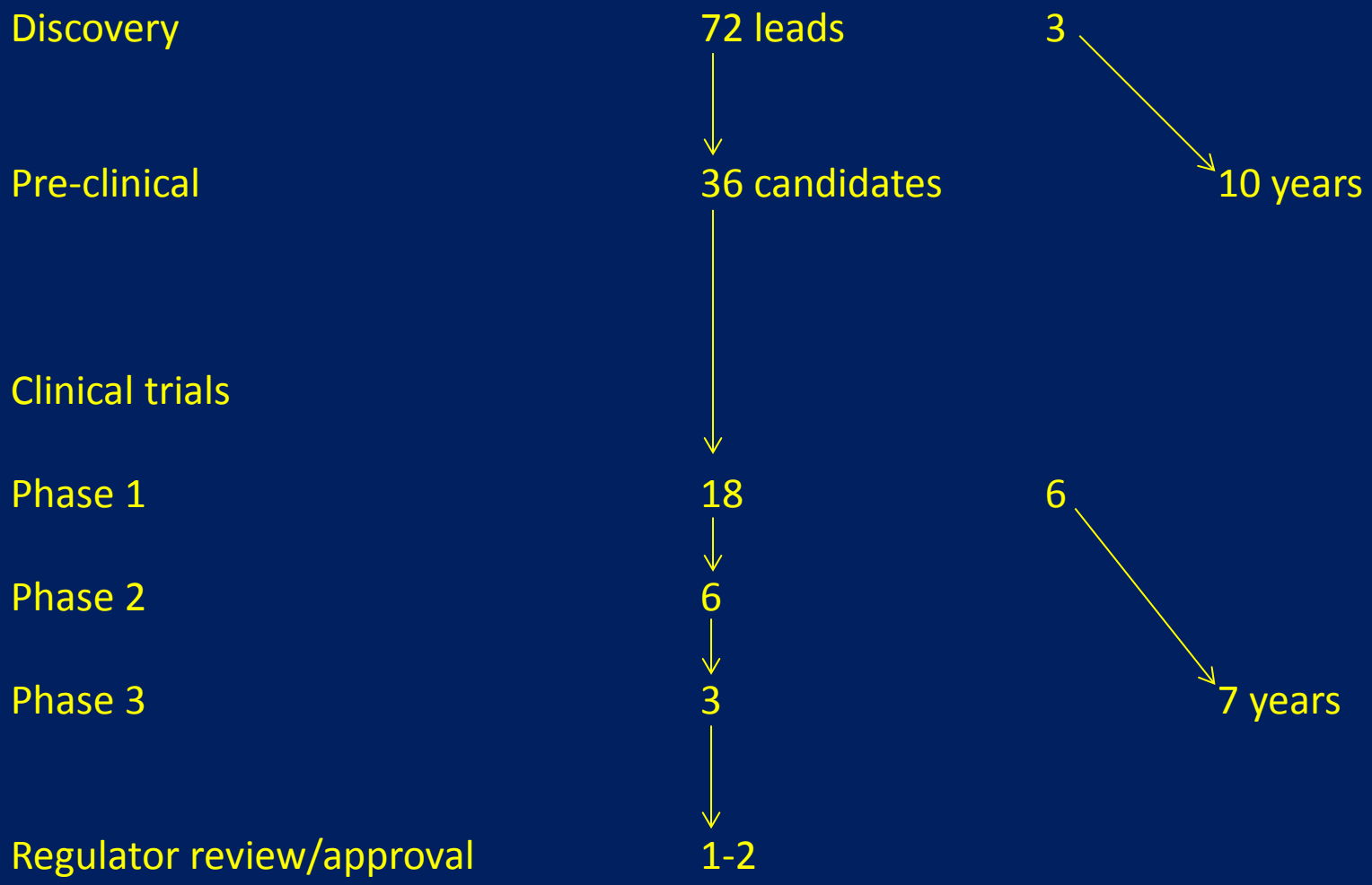
| Year | Active programme |
|---|---|
| 1940 | 1 |
| 1950 | 4 |
| 1960 | 9 |
| 1970 | 22 |
| 1980 | 26 |
| 1990 | 29 |
| 2000 | 31 |
| 2010 | 12 |
| 2013 | 9 |

## Why are there so few drugs and companies?

- Few novel modes of action
- Increasing regulatory demands (manufacture, safety, efficacy)
- Trial designs (superiority vs non-inferiority)
- Infection control interventions
- Highly saturated market
- High generic competition
- Conservative prescribers
- Short course therapy
- Cost containment
- Antimicrobial resistance

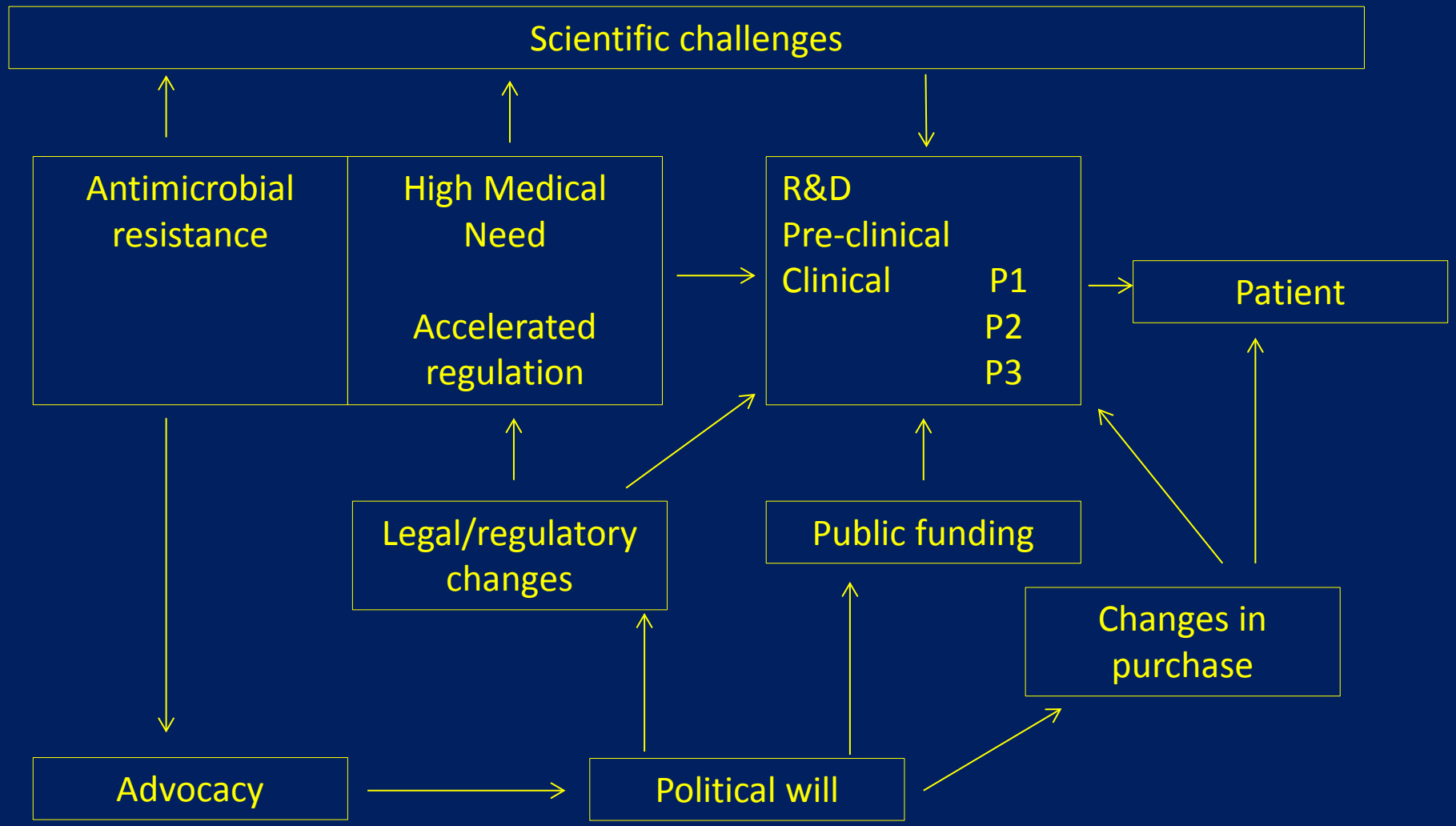
- Means less attractive commercially than other therapeutic areas

## Drug development takes a long time (Paul et al, 2010; Rex, 2015)




Start now and you may have approval by 2025-2030

## Determinants impacting on research and development (Harbarth et al, 2015)



## Actual and Proposed Changes in regulatory system

- Accelerated approval

  FDA QIDP (Qualified Infectious Disease Product) designation – limited approval after Phase 2 studies (ceftazidime-avibactam, AZ)

- Changes to Phase 3 development

  Tier A Disease focus, two RCTs P3 for each indication, large number of patients; few resistant pathogens

  Tier B Single disease focused RCT P3 per indication supported by smaller pathogen/resistance specific studies, may be prospective comparative, open label data sets ± historic data, PK-PD studies

  Tier C Smaller syndrome or pathogen specific trials as Tier B. No large RCTs

  Tier D Animal Rule Studies – no clinical data, i.e. Anthrax

- Safety only Studies

  Large non-comparative studies safety data only collected historically used in Phase 4 development

## Drugs in Development (1)

## Major antibacterial drug research and development programmes and phase of development – 2015

| | Phase 1 | Phase 2 | Phase 3 | All |
|---|---|---|---|---|
| Old mode of action; G+ | 2 | 4 | 3 | 9 |
| Novel; G+ | 2 | 3 | - | 5 |
| Old; G- | 2 | 4 | 3 | 9 |
| Novel G- | 1 (Pseudomonas only) | | | 1 |

Theuretzbacher 2015

## Drugs in Development (2)

| | EMA status |
|---|---|
| Ceftazidime+avibactam (AZ) | under review |
| Ceftolozane+tazobactam (Merck) | approved 2015 |
| Ceftobiprole (Basilea) | approved 2013 |
| Oritavancin (T Medicines Co) | approved 2015 |
| Tedizolid (Merck) | approved 2015 |
| Dalbavancin (Allegan) | approved 2015 |

Phase 3

Meropenem+RPX7009 (The Medicines Co)
Eravacycline (Tetraphase)
Plazomicin (Achaogen)
Delafloxacin (Melinta)
Solithromyciin (Cempra)
Omadacycline (Paratek)
Lefamulin (BC-3781) (Nabriva)
Bay 41-6551-inhal amikacin (Bayer)

Phase 2

Nemonoxacin; radezolid; avarofloxacin; brilacidin, AFN 1252, POL 7080; aztreonam-avibactam; imipenem+MK-7655, Debio 1450/2, EXT 0914; S 649266, CG 400549; finafloxacin; zabofloxacin

**Future issues:**

1) Antimicrobial resistance emergence- uncertainty

2) Value of antibacterials – companies patients and society – sales and revenue

3) Cost of development – financial models and net present value

## 1) Antibiotic Resistance

- Improved dosing and use of combinations
- Rigorous infection control

vs

- Resistance as emerged to all drugs
- Use leads to resistance
- Rapid outbreaks are always possible

→ uncertainty remains, difficult to cost

## 2) Two types of antibiotic value

- Present – use them to treat infection now (this model drives company revenues)
- Future – the agent is available to use in the future

## 3) Cost of development

Simple approach

Years 1-13 development costs - €600m
Years 13-33 on market sales - €2,500m

Net present value (NPV)

- Cash today is worth more than the promise of cash tomorrow

- Based on cost of capital, risk etc, typical discount is 10% pa, hence €100 in ten years time is worth €39 today

and NPV >0 means some value demonstrated

applied above from year 0 the NPV is - €50m for antibacterials

## US/EU economic modelling

For:-

- ABOM, ABSSI, CAP, cIAI, cUTI, HAP-VAP
  NPV always <USD 40m

However:-

- For patient population value much higher – USD 12B

Sertkaya et al

## Cost of Development: Mitigation

## Public – Private Partnerships (1)

USA:
NIAID: Antibacterial Resistance Programme

- Extensive assay pre-clinical services
- Phase 1 units
- Antibacterial Resistance Leadership Group
- Master protocols

BARDA: (Biomedical Advanced Research & Development Authority)

- Several public-private partnerships, i.e. eravacycline (Tetraphase); Plazomicin (Achaeogen); Aztreonam-avibactam (AZ)

## Cost of Development: Mitigation

## Public – Private Partnerships (2)

EU - Innovative Medicines Initiative (IMI) ND4BB Programme (New drugs for Bag Bugs)

Topic 1: COMBACTE-NET
- > Clinical & Laboratory network and infrastructure
- > Analytical network
- > Clinical development of GSK 1322323

Topic 2 TRANSLOCATION
Basic Sciences Research on Gram-negatives – efflux and cell wall penetration

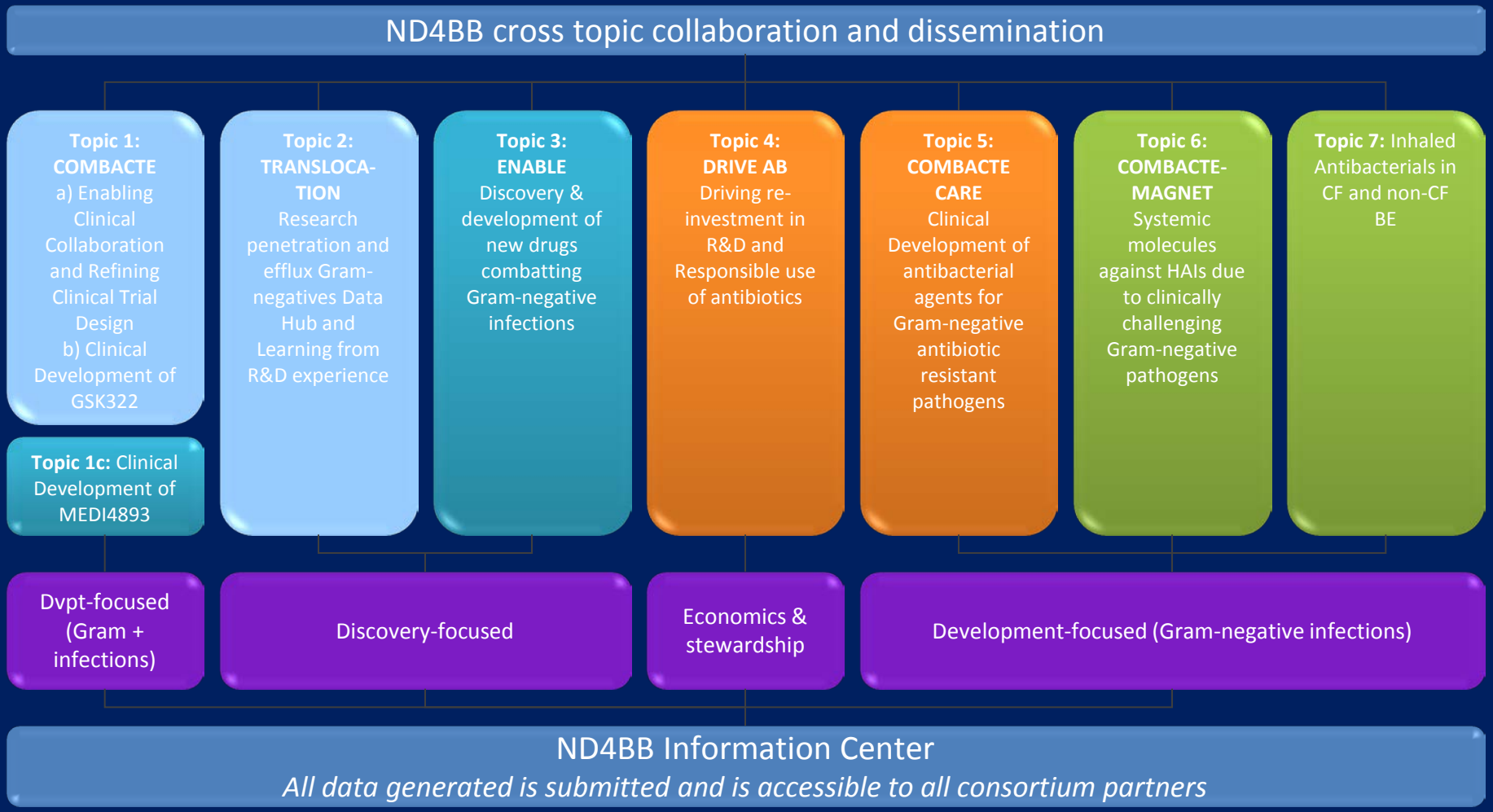
Topic 3 ENABLE
Discovery and Development of New Drugs combatting Gram-negative infection.
Target to candidate research including Phase 1

Topic 4 DRIVE-AB
Driving re-investment in R&D and responsible use of antibiotics

Topic 5 COMBACTE-CARE
Clinical development of antibacterial agents for Gram-negative antibiotic resistant pathogens aztreonam+avibactam

Topic 6 COMBACTE-MAGNET
Systemic molecules against HCAI due to clinically challenging Gram-negative pathogens – Phase 1/2 AIC499

# The ND4BB Programme



# Example: COMBACTE-MAGNET

- To prevent infections caused by *Pseudomonas aeruginosa* in critically ill patients
  - Clinical development of MEDI3902, a bivalent bispecific IgG1 mAb targeting the pathogenic components PsI and PcrV

- To treat infections caused by MDR Enterobacteriacae, *Pseudomonas aeruginosa* and Acinetobacter species
  - Clinical development of AIC499, a new beta-lactam alone or in combination with a beta-lactamase inhibitor

- To establish an epidemiologic network able to map and organize available surveillance systems in Europe (« EPI-Net »)

# The COMBACTE-MAGNET Consortium

**41 partners** (5 pharma and 36 public partners)

CHUL
INSERM
ECRIN
APHP
ICAN

UA
SLUC

TAU

UKL-FR
EKUT
UULM

CEFAIA
MUW

UMCU
JC
AMC
EMC
RUNMC

NBT
UOXF
UCL
Bristol
UWE
SGUL
PENTA-ID
EGFCP
ULIV
TranScrip
RLBUHT

UTARTU

SAS
SERMAS
IDIBAPS
HUSE
ICS-HUB

UNIGE
UZH
CHUV

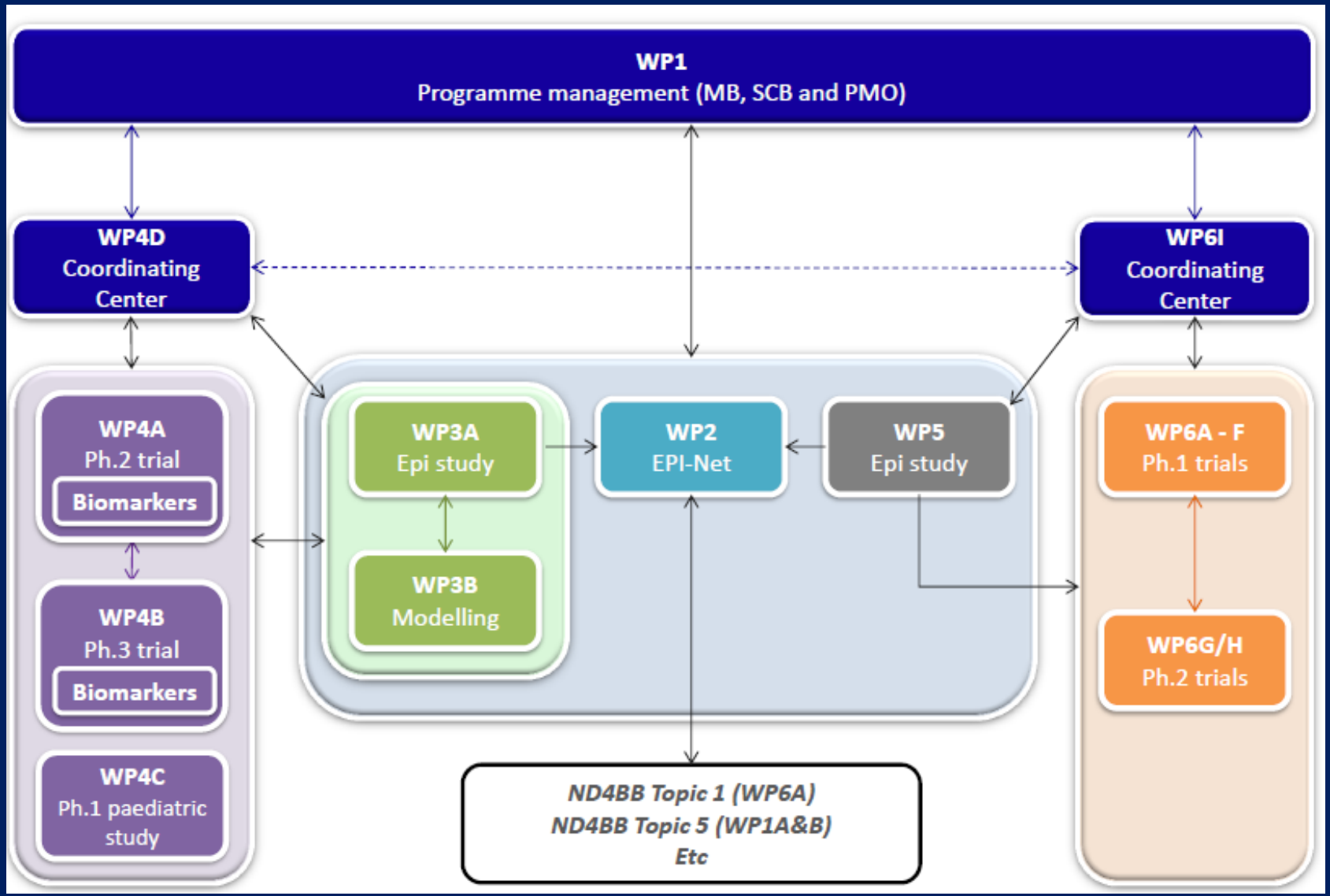
AiCuris
Anti-infective Cures

gsk

SANOFI

basilea
PHARMACEUTICA

# Relationship between COMBACTE-MAGNET WPs



# Staff Efforts

| Participant No. / Short name | Total person months |
|---|---|
| Part.1/AZ/MI | 2724.99 |
| Part.2/UMCU | 400.04 |
| Part.3/UA | 412.42 |
| Part.4/UNIGE | 100.58 |
| Part.5/Julius Clinical | 0 |
| Part.6/ECRIN-ERIC | 0 |
| Part.7/EKUT | 527 |
| Part.8/RUNMC | 104 |
| Part.9/SAS | 153 |
| Part.10/UKL-FR | 97.81 |
| Part.11/UOXF | 12 |
| Part.12/UULM | 38 |
| Part.13/UZH | 38 |
| Part.14/ICAN | 57.60 |
| Part.15/IDIBAPS | 72 |
| Part.16/CHUV | 20.88 |
| Part.17/SERMAS | 57.60 |
| Part.18/UCL | 66.60 |
| Part.19/PENTA ID | 20.92 |
| Part.19a/SGUL | 70.11 |
| Part.19b/Utartu | 28.8 |
| Part.20/EGFCP | 13.33 |

| Participant No. / Short name | Total person months |
|---|---|
| Part.21/AMC | 24 |
| Part.22/HUSE | 36 |
| Part.23/CHUL | 67.20 |
| Part.24/INSERM | 122 |
| Part.25/AiCuris | 600.35 |
| Part.26/NBT | 728.27 |
| Part.27/TAU | 38.00 |
| Part.28/EMC | 29.00 |
| Part.29/ULIV | 30.00 |
| Part.30/TranScrip | 0.80 |
| Part.31/Bristol | 195.62 |
| Part.32/CEFAIA | 30.04 |
| Part.33/ICS-HUB | 14.00 |
| Part.34/MUW | 54.00 |
| Part.35/GSK | 8.40 |
| Part.36/ Basilea | 8.40 |
| Part.37/ Sanofi | 8.40 |
| Part.38/APHP | 28.00 |
| Part.39/RLBUHT | 20.00 |
| Part.40/UWE | 39.00 |
| Part.41/SLUC | 49.60 |

# Phase 1 – Work Packages

- WP6A: Single and Multiple dose trial of AIC499 in healthy volunteers (Part A) and afterwards generation of early safety and microbiological efficacy data of AIC499/BLI from patients with cUTI without pyelonephritis (Part B)
- WP6B: Drug-drug interaction trial between AIC499 and BLI to investigate their mutual influence on pharmacokinetics and safety
- WP6C: Pharmacokinetics and mass balance study of AIC499, and identification of its metabolites in humans
- WP6D: TQT prolongation study to obtain guidance for cardiac safety monitoring in studies with larger populations
- WP6E: Drug-drug interactions between AIC499/BLI and usual concomitant medication in the intended indications
- WP6F: Effect of different degrees of renal impairment in patients on the pharmacokinetics of AIC499

# Phase 2 – Work Packages

- **WP6G**: PoC trial in hospitalised patients with cUTI due to Gram-negative pathogens
- **WP6H**: PoC trial in hospitalised patients with cIAI due to Gram-negative pathogens
  - To investigate the safety, tolerability, efficacy and pharmacokinetics/ pharmacodynamics of AIC499/BLI in patients with cUTI or cIAI
  - To assess the efficacy of AIC499/BLI in cases caused by multi-drug resistant Gram-negative pathogens
- **WP6I**: Clinical workstream (WP6A-H) coordination cente
  - To provide program management and project coordination, and to ensure strategic alignment within WP1, and with other programs within ND4BBs

## Possible future economic ideas

(Push) Refundable tax credits

- For some percentage (i.e. 25%) of qualifying expenses, company either receives a tax credit or payment.

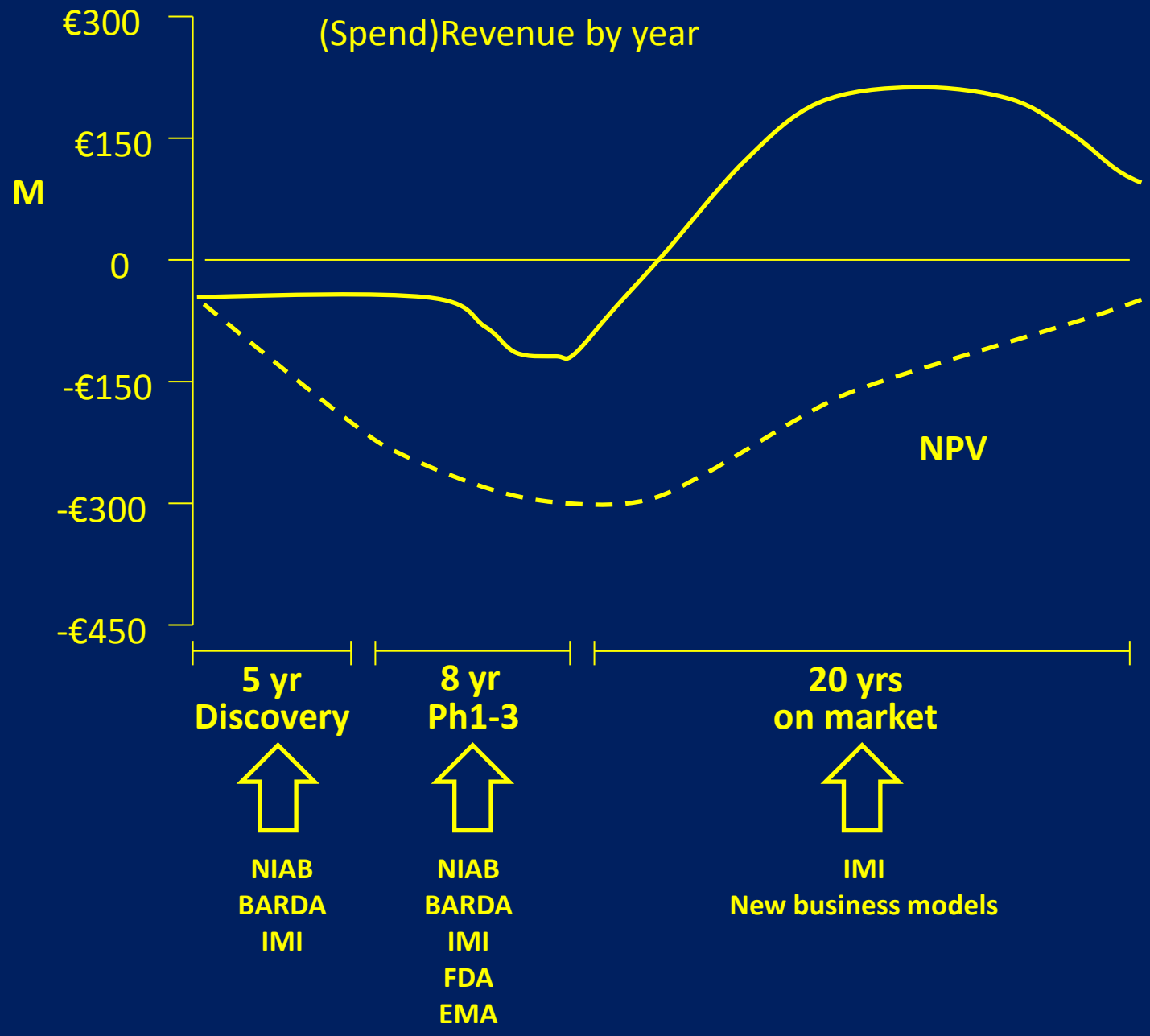
- Immediate impact on NPV, i.e. €150m returned to company of development costs of €600m

Pull (Insurance – based approaches)

- National acquisition at a fixed predictable rate, i.e. UK by £10m/year new antibiotic for 10 years

- Fee guarantees availability of drug whether used or not.

# Economic impacts



**Conclusions:**

- Antibacterial drug development is changing and will change more
- Massive public sector investment is going into this area in both the US (BARDA) and EU (IMI)
- Regulatory change is helping drug development
- The number of new agents entering development is increasing – but few novel modes of action
- Breaking out of the sales drives profits model is essential for future development
- Antibiotic Stewardship in the NHS is not yet responsive to new agents
- Unclear how sustainable development will be achieved