IMI New Drugs for Bad Bugs The COMBACTE-NET, COMBACTE-CARE, COMBACTE-MAGNET Consortium

MARC BONTEN

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The typical phase III trial with a new antibiotic (through the eyes of a clinical physician)

- Design usually not really appreciated by clinicians/investigators (too rigid, not addressing the target population, too many exclusion criteria....)
- No/little direct interaction between the pharmaceutical company and investigators, most interaction through a global CRO CRA
- No/few possibilities to add (clinically relevant) substudies to main trial
- >80% of the initiated sites do not enroll a single patient
- Study takes ages (at least much longer than planned)
- Quality of data collection may be suboptimal



Innovative Medicines Initiative (IMI): a new way to collaborate

The largest public-private partnership in life science R&D



- IMI1 Started in 2008, ended in 2014
 - 11 Calls launched





Innovative Medicines Initiative (IMI): a new way of working

Main objectives:

- Accelerating the development of safer and more effective medicines for patients in Europe
- Boosting the biopharmaceutical sector in Europe
- Creating a collaborative environment for academia, industry, SMEs, regulators, patients

ND4BB is part of the Action plan against the increased threats from AMR launched by the European Commission in November 2011

ND4BB Vision: Delivering a pipeline of new antibacterial agents to patients



Overall Architecture of the ND4BB Programme



Timeline and total budget estimation of the seven topics of the ND4BB programme (EFPIA contribution)





ND4BB-EFPIA Partners

COMBACTE-NET	• GSK, AZ-Medi, Da Volterra, Medicines Company, Janssen	
COMBACTE-CARE	• AZ-Medi, GSK, Basilea	
COMBACTE-MAGNET	• AZ-Medi, Aicuris, Basilea, GSK, Sanofi	
TRANSLOCATION	• GSK, Sanofi, AZ-Medi, Basilea, Janssen	
ENABLE	• GSK, Sanofi, AZ-Medi, Basilea	
DRIVE-AB	• AZ-Medi, GSK, Astellas, Pfizer, Roche, Sanofi,	
i-ABC	• Novartis, Basilea	

Objectives

COMBACTE-NET/COMBACTE-CARE/COMBACTE-MAGNET

Create a self-sustaining antibacterial development network

- Expanding research and laboratory networks
- Optimal alignment of clinical trials with investigator sites
- Obtain clinical and epidemiological data

Increase efficiency of antimicrobial drug development

- Align clinical trials with cutting edge molecular mehodologies and trial design
- Deliver clinical trials with various candidate compounds from MedImmune/Astra Zeneca, Aicures, Astra Zeneca, Da Volterra, Medicines Company

The 4 pillars of the COMBACTE projects

CLIN-Net

High-quality clinical research network in all European countries with certification criteria and GCP Training program (lead: UMC Utrecht, M. Bonten)

LAB-Net

High-quality laboratory network in all European countries with assessment of existing laboratory methods, quality assessment system, specimens and strains repository (lead: U of Antwerp, H. Goossens)

STAT-Net

Network to improve clinical trials delivery, perform advanced biostatistical and PK/PD modelling studies, evaluate novel clinical design strategies using modern biostatistical concepts (lead: U of Geneva, S. Harbarth)

EPI-Net

Network to identify and map existing surveillance systems, to establish frameworks for data collection to support antibacterial drug development (lead: U of Tuebingen, E. Tacconelli)

All Academic & EFPIA partners



All Academic partners

- COMBACTE
- COMBACTE-MAGNET
- COMBACTE-CARE
- 2 or 3 projects

CLIN-Net & LAB-Net in numbers April 2016 40 countries **483** cities 724 hospitals 1411 hospital contacts **506** laboratories 656 lab contacts

CLIN-Net GCP Course

Adequate execution of trials is essential in maintaining our network of investigators that can perform high quality clinical trials.



Helping member sites in reaching and maintaining full GCP / ICH compliance.



- **Interactive**: Participants are challenged to compare GCP principles to their daily practice and discuss various cases with their fellow course participants, with UMCU moderators available for assistance.
- **Flexible**: The course can be paused and resumed during one month.



- Available since June 2014.
- In collaboration with European Forum for GCP (EFGCP).



Compliant with TransCelerate and PharmaTrain.



Self-reported GCP Training status of Clinical Investigators in CLIN-Net

Year of completion training	% of investigators
2014-2015	31.5
Before 2014	15.4
Unknown	1.6
Not GCP trained	51.5

Excluding Clinical Investigators trained by CLIN-Net (n=12)



Investigators trained by CLIN-Net

Year	Online GCP course	Face to face GCP courses
2016 (up to 1 April)	73	0
2015	96	55
2014	38	22
Total	207	77

What does a network look like?













Network Management System Feasibility Questionnaire Tool

- Research Online data management system, questionnaire tool Network Management System (NMS): COMBACTE
 - Database
 - Contact information, trial experience, site facilities, epidemiology
 - Data from baseline- and trial feasibility questionnaires
 - Data from NMS can be updated by participants to ensure accurate information
- Optimizes site selection, facilitates communication with sites
 - Feasibility questionnaires prefilled from NMS / previous questionnaires
 - Search and selection tools for reporting and trials
 - 2226 questionnaires sent out, 1137 have been completed
 - Minimal work load for member sites is one of the key objectives

Ongoing studies

- SAATELLITE (AZ/MedImmune; Academic lead Bruno Francois, Limoges)
 - DB placebo-controlled phase II RCT; estimated sample size = 462
 - To evaluate in mechanically ventilated ICU patients
 - safety, tolerability, and pharmacokinetics of MEDI4893
 - effects of MEDI4893 on the incidence of *S. aureus* pneumonia
 - biomarkers associated with S. aureus disease severity and outcome
- ASPIRE-ICU (AZ/MedImmune; Academic lead Jan Kluytmans, Utrecht)
 - Observational study; estimated sample size = 2x2000
 - To determine
 - incidence of and risk factors for S. aureus and P. aeruginosa for ICU pneumonia
 - the role of antibodies against Gram-positive and Gram-negative bacterial virulence factors as biomarkers of disease risk and outcome
- EURECA (AZ; Academic lead Jesus Rodriguez Bano, Seville)
 - Observational study; estimated sample size = 800
 - To assess the clinical management and outcomes of patients with MDR-GNB infections

Ongoing studies

- REJUVENATE (AZ; Academic lead Oliver Corneli, Cologne)
 - Phase II PK-PD study with AZT-AVI (Aztreonam-Avibactam); estimated sample size = 40
 - Dose finding for global phase III study
 - Microdialysis substudy
- EVADE (AZ/MedImmune; Academic lead Jean Chastre, Paris)
 - DB placebo-controlled phase II RCT; estimated sample size = 492
 - To evaluate in mechanically ventilated ICU patients
 - safety, tolerability, and pharmacokinetics of MEDI3902, a bi-specific antibody
 - effects of MEDI3902 on the incidence of P. aeruginosa pneumonia
 - biomarkers associated with P. aeruginosa disease severity and outcome
- RESCUING (Aicuris; Academic lead Miguel Pujol, Barcelona)
 - retrospective study on UTI; estimated sample size = 1000
 - Estimating incidences for subsequent trials with antibiotic from Aicuris

CLIN-Net & LAB-Net Study preparation and execution

Studies	Approached	Questionnaire completed	Selected	Initiated	Enrolling
COMBACTE-N	ET				
ASPIRE-ICU	164	42	21	7	3
SAATELLITE	955	177	101	62	25
COMBACTE-CA	ARE				
EURECA	139	81	50	-	-
REJUVENATE	37	29	22	1	-
COMBACTE-M	AGNET				
EVADE	229	127	70	1	-
RESCUING	48	31	21	21	18



The COMBACTE pipeline

					Q3/2014	1 201	5	201	5		2017			2018	;	
	ASPIRE-ICU	AZ/MI	ICU_VAP	Epi						101/	2000					
	ASPIRE-SSI	AZ/MI		Epi										0/50	00	
COMPACTE	SAATELLITE	AZ/MI	ICU	RCT					76/462							
	WP6C SSI	AZ/MI		RCT												
NEI	WP6E tbd	AZ/MI	ICU	RCT												
	WP7	DaV		Epi						1	000					
	WP8	MedComp	ICU	RCT												
COMBACTE	EURECA	AZ		Epi		_				800						
CARE	REJUVENATE	AZ	ICU+	RCT								40				
_	WP2B	AZ	ICU+	RCT						_	·				400	
	ASPIREICU	A7/MI	ICU VAP	Fni						5	000					
	FVADE	AZ/MI	ICU VAP	RCT		_							492			
СОМВАСТЕ	WP4B	AZ/MI	ICU VAP	RCT											98	0
MAGNET	RESCUING							273	/1000							-
	WP6G	AiCuris	cUTI	RCT							l			in di		240
	WP6H	AiCuris	cIAI	RCT												225
	WP3		ARBO	Epi			_								1	.500
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Shionogi study

- Multicenter, randomized, open-label clinical trial of a new siderophore cephalosporin or Best Available Therapy (includes combination of antibiotics) to treat severe infections caused by Carbapenem-resistant Gram-negative Pathogens.
- Type of infection: HAP/VAP, cUTI, sepsis/BSI
- 150 patients in EU & non-EU sites
- Question: Assistance in selecting 50 suitable clinical and laboratory sites in Europe



Shionogi study



COMBACTE Events



CLIN-Net & LAB-Net events

Presence at Medical Conferences	GCP / Lab Training	Investigator Meetings
ECCMID 2016- Amsterdam, Holland	GCP Training Face to Face - Budapest Hungary, 13-14 April 2016	EVADE Investigator Meeting – Paris, France
ECCMID 2015- Copenhagen, Denmark	LAB-Net detection of carbapenem-resistant Gram-negatives – Belgrade, Serbia, 2015	REJUVENATE Investigator meeting – Frankfurt, Germany
ECCMID 2014- Barcelona, Spain	GCP Training Face to Face- Madrid, Spain, 2015	EURECA Investigator Meeting- Belgrade, Serbia
ECCMID 2013- Berlin, Germany	GCP Training Face to Face, Belgrade Serbia, 2015	COMBACTE Investigator Meeting- Copenhagen, Denmark
SRLF 2016, - Paris, France	LAB-Net workshop on Antibiotic resistance – Skopje, Macedonia, 2014	COMBACTE Investigator Meeting- Barcelona, Spain
CESAR 2015- Sibenik , Croatia	LAB-Net workshop on Antibiotic resistance – Pristina, Kosovo, 2014	COMBACTE Investigator Meeting,- Berlin, Germany
DKOU 2015- Berlin, Germany	GCP Training Face to Face- Grindelwald, Switzerland, 2014	SAATELLITE Investigator Meeting- Vienna, Austria
Hungarian Society of Clinical Microbiology and Infectious Diseases 2015 - Szolnok, Hungary		
UKCCRF meeting-Cardiff, United Kingdom		
KNVM_NVVM 2014, Antwerpen, Belgium		
Hungarian Society of Clinical Microbiology and Infectious Diseases 2014 - Debrecen, Hungary		

WWW.COMBACTE.COM

COMBACTE-NET COMBACTE-MAGNET COMBACTE-CARE

Combatting Bacterial Resistance in Europe

STAT-Net

About CO	MBACTE	COMBACT	TE 2016:	GCP	
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ntimicrobial resi rowing problem ith few new dru arket, there is a ew medicines to fections.	stance (AMR) is a worldwide, and gs making it to the n urgent need for treat resistant	realization ND4BB vis 03/31/2016: The General Assembli three COMBACT COMBACTE-NET	of the sion 2016 Annual y meeting for the E consortia , COMBACTE-	To assure a Euri infrastructure pe quality clinical tri antibiotic resista participants are comply with 'Go Practices' (GCP).	opean resea erforming hig ials related to nce, all CLIN required to od Clinical
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LAB-Net

CLIN-Net



EPI-Net

& MICROBIOLOGIST

DRIEKE

Innovative Medicines Initiative and antibiotic resistance

Antibiotic resistance is broadly recognised as a growing global public-health burden.^{1,2,3} The effect of infections caused by multidrug resistant (MDR) bacteria, together with insufficient development of new antibiotics is a societal problem that needs a societal response—1 million deaths could occur as a result of MDR infections by 2025.⁴ With few new effective antibiotics in the pipeline, particularly against Gram-negative

microorganisms, this antibiotic armageddon could reach unprecedented proportions and imminent action is needed to address this public-health crisis. One of the major undertakings to address the challenges of developing new antibacterial therapies is the creation of public-private partnerships (PPPs), which are successful models for moving drug development forward in areas of unmet medical needs.



www.thelancet.com/infection Vol 15 December 2015

The Innovative Medicines Initiative's New Drugs for Bad Bugs programme: European public—private partnerships for the development of new strategies to tackle antibiotic resistance

T. Kostyanev¹, M. J. M. Bonten², S. O'Brien³, H. Steel⁴, S. Ross⁴, B. François⁵, E. Tacconelli⁶, M. Winterhalter⁷, R. A. Stavenger⁸, A. Karlén⁹, S. Harbarth¹⁰, J. Hackett¹¹, H. S. Jafri¹², C. Vuong¹³, A. MacGowan¹⁴, A. Witschi¹⁵, G. Angyalosi¹⁶, J. S. Elborn¹⁷, R. deWinter² and H. Goossens^{1,18*}

J Antimicrob Chemother 2016; **71**: 290–295

The future of CLIN-Net, LAB-Net, STAT-Net, EPI-Net





Federation of the International Fight against Antibiotic resistance







The future of CLIN-Net, LAB-Net, STAT-NeT, EPI-Net



In 1962, Henri Tagnon founded the Groupe Européen de Chimiothérapie Anticancéreuse (GECA) with a group of European experts and visionaries aware of the importance of introducing a multidisciplinary approach and international cooperation in clinical research in Europe. In 1968, this successful initiative developed into the current **EORTC**.

Currently, the EORTC is both multinational and multidisciplinary and comprises over 300 hospitals and cancer centres in over 30 countries which include some 2,500 collaborators from all disciplines involved in cancer treatment and research.

Presented on behalf of.....



Offial COMBACTE video









Stay informed: COMBACTE Newsletter





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COMBACTE

Newsletter

Combatting Bacterial Resistance in Europe

Adressing AMR Head-on

Bevenie events and reports in the past weeks, months and years have had an important influence on the avestness of the global threat of antimicrobial resistance. AlOurs is committee to addressing the antibiotic resistance threat and we are excited to have the opportunity to collaborate with world-removing academic pathesis in such an innovative way of antibiotic development. The ODMBACTE-MAXNET consolium kick-eth meeting took place alimost a year ago and all teams have progressed guide well in their respective work packages time mean.

Reflections on 2015

As another year daws to a close it allows us time for relation on which has been a challenging but i vouid say another successful year for COMEACTE not only with regards to Lacket, Bishett, Clin-Net and the orgoing clinical this but also with regards to the Open Call process which is finally nearing competent. We started the year with a large gap in COMEACTE following the termination of the development of GMS22 and set outselves the aggressive goal of bringing new patheres with novel clinical tables in COMEACTE to fill that gap by the end of the year littles.



EVADE



It is with great pleasure that the COMBACTE-MARNET WP4A team announce the new name for the phase 2 Prodo-HOoncest safety and efficacy study of MEDI390C in patients at high risk of developing Persubnomas arruginosa per Rectancially Ventilated Bulgects) <u>interment</u>.



COMBACTE at Réanimation

From the 13th to the 13th of January, the Bocieté de Retainmidion de Langue Francise (BRLF) is holding lis annual congres Réarimation 2016 di Pata Esco. - Potto de Vesallies, Patis, This cognes for Penchspeaking Intensivist will welcome many of the French, Beiglan and Swiss investigeous the eat, or will be, Innovate in the COMBACTE ICU studies, such as 8AATELLITE and the upcoming EVAGE immun.



Infectious disease leads in first phase of Europe's IMI effort



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