This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 101015736

EU-RESPONSE

WORKSHOP COORDINATION OF PUBLICLY FUNDED CLINICAL TRIALS

MAYA HITES[1], MD, PhD AND INGE CHRISTOFFER OLSEN[2], PhD

FOR THE EU-RESPONSE CONSORTIUM

14 MAY 2024

1. Hôpital Universitaire de Bruxelles (HUB), ULB, Belgium
2. Dept. Research for Clinical Trials, Oslo University Hospital, Norway

An ultramarathon against time


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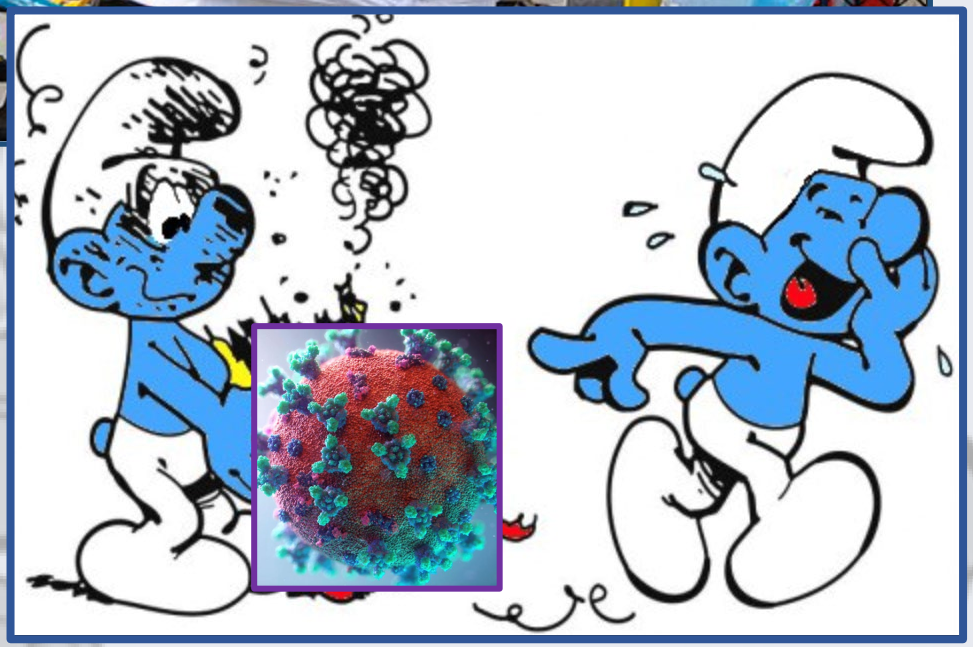


EU RESPONSE

eu-response.eu

HOME | THE PROJECT | CONSORTIUM | DISCOVERY | EU-SOLIDACT | NEWS & EVENTS | RESULTS | CONTACT US | MEMBERS AREA

EUROPEAN RESEARCH AND PREPAREDNESS NETWORK FOR PANDEMICS AND EMERGING INFECTIOUS DISEASES

EU-RESPONSE is funded by the European Union's Horizon 2020 research and innovation programme.

Firstly, the project focuses on the expansion of the DisCoVeRy trial in Europe, to test potential treatments for COVID-19. Secondly, based on the experience acquired from DisCoVeRy, EU-RESPONSE aims to design and run a new adaptive European platform trial for emerging infectious diseases, called EU-SolidAct, thus improving Europe's responsiveness to pandemic crises.

Read more

H2020 grant
15.7 M€

2020- 2025

21
Partners

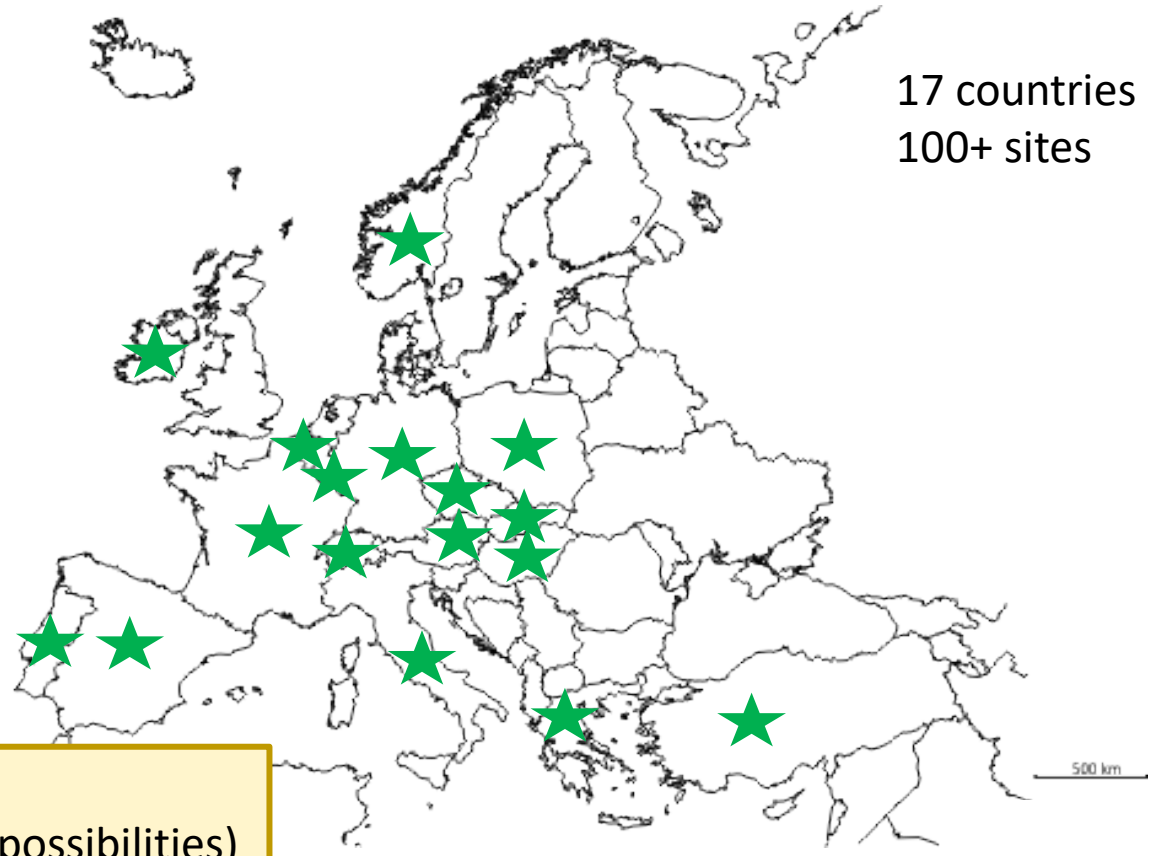
16
Countries

Objectives

- Expand DisCoVery
- Build a multinational, European multi-arm COVID-19 platform trial beyond DisCoVeRy (WP2): **EU-SolidAct**
- Develop a network of hospitals to conduct clinical trials evaluating treatment strategies in patients with COVID-19 and **other emerging infectious diseases**
- Website: www.eu-response.eu

EU-RESPONSE

Trial	Inclusions
DisCoVeRy	1546
EU-SolidAct	290
Total	**1836**



17 countries
100+ sites

DISCOVERY

EU SOLIDACT
Part of EU-RESPONSE

Master protocoles for phase 2 and phase 3 trials
with adaptive levels of participation (with or without biobanking possibilities)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

JOURNAL OF INFECTION

Articles Publish About Contact

LETTER TO THE EDITOR / VOLUME 88, ISSUE 3, 106120, MARCH 2024

Download Full Issue

Tixagevimab-cilgavimab (AZD7442) for the treatment of patients hospitalized with COVID-19 (DisCoVeRy): A phase 3, randomized, double-blind, placebo-controlled trial

Maya Hites [1] • Clément R. Massonnaud [2] • Eva Larranaga Lapique • ... France Mentré [3] • Florence Ader [1] • on behalf of the DisCoVeRy study group • Show all authors • Show footnotes

Open Access • Published: February 15, 2024 • DOI: https://doi.org/10.1016/j.jinf.2024.106120 •

J Antimicrob Chemother 2022; **77**: 1404–1412
https://doi.org/10.1093/jac/dkac048 Advance Access publication 2 March 2022

Journal of Antimicrobial Chemotherapy

Effect of remdesivir on viral dynamics in COVID-19 hospitalized patients: a modelling analysis of the randomized, controlled, open-label DisCoVeRy trial

Guillaume Lingas [1*†], Nadège Néant[1†], Alexandre Gaymard[2,3], Drifa Belhadi[1,4,5], Gilles Peytavin [1,6], Maya Hites[7], Thérèse Staub[8], Richard Greil[9,10,11], Jose-Artur Paiva[12,13], Julien Poissy[14], Nathan Peiffer-Smadja [1,15,16], Dominique Costagliola[17], Yazdan Yazdanpanah[1,15], Florent Wallet[18,19], Amandine Gagneux-Brunon [20,21,22], France Mentré[1,4,5,23], Florence Ader[19,24], Charles Burdet[1,4], Jérémie Guedj [1§] and Maude Bouscambert-Duchamp[2§] on behalf of the DisCoVeRy study group

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IDSA hivma OXFORD

Clinical Infectious Diseases

MAJOR ARTICLE

Cardiac Adverse Events and Remdesivir in Hospitalized Patients with Coronavirus Disease 2019 (COVID-19): A Post Hoc Safety Analysis of the Randomized discovery Trial

Vida Terzić[1,2], Joe Miantezila Basilua[1,2], Nicolas Billard[3], Lucie de Gastines[1,2], Drifa Belhadi[3,6], Claire Fougerou-Leurent[4], Nathan Peiffer-Smadja[5,6], Noémie Mercier[1,2], Christelle Delmas[7], Assia Ferrane[7], Aline Dechanet[3], Julien Poissy[8], Hélène Espérou[7], Florence Ader[9], Maya Hites[10], Claire Andrejak[11], Richard Greil[12], José-Artur Paiva[13], Thérèse Staub[14], Evelina Tacconelli[15], Charles Burdet[3], Dominique Costagliola[16], France Mentré[3,6], Yazdan Yazdanpanah[4,5,17], Alpha Diallo[1,2], and the DisCoVeRy study group*

Clinical Microbiology and Infection 28 (2022) 1293–1296

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

CMI CLINICAL MICROBIOLOGY AND INFECTION

Letter to the Editor

An open-label randomized, controlled trial of the effect of lopinavir and ritonavir, lopinavir and ritonavir plus interferon-β-1a, and hydroxychloroquine in hospitalized patients with COVID-19: final results

Florence Ader*, The DisCoVeRy Study Group

Trasoeid et al. Critical Care (2023) 27:9
https://doi.org/10.1186/s13054-022-04205-8

Critical Care

RESEARCH Open Access

Efficacy and safety of baricitinib in hospitalized adults with severe or critical COVID-19 (Bari-SolidAct): a randomised, double-blind, placebo-controlled phase 3 trial

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ARTICLE

Association between SARS-CoV-2 viral kinetics and clinical score evolution in hospitalized patients

Nadège Néant[1] | Guillaume Lingas[1] | Alexandre Gaymard[2,3] | Drifa Belhadi[1,4] | Maya Hites[5] | Thérèse Staub[6] | Richard Greil[7,8,9] | Jose-Artur Paiva[10,11] | Julien Poissy[12] | Nathan Peiffer-Smadja[1,13,14] | Dominique Costagliola[15] | Yazdan Yazdanpanah[1,13] | Maude Bouscambert-Duchamp[2] | Amandine Gagneux-Brunon[16,17,18] | Florence Ader[19,20] | France Mentré[1,4] | Florent Wallet[21] | Charles Burdet[1,4] | Jérémie Guedj[1] | the DisCoVeRy study group

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Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial

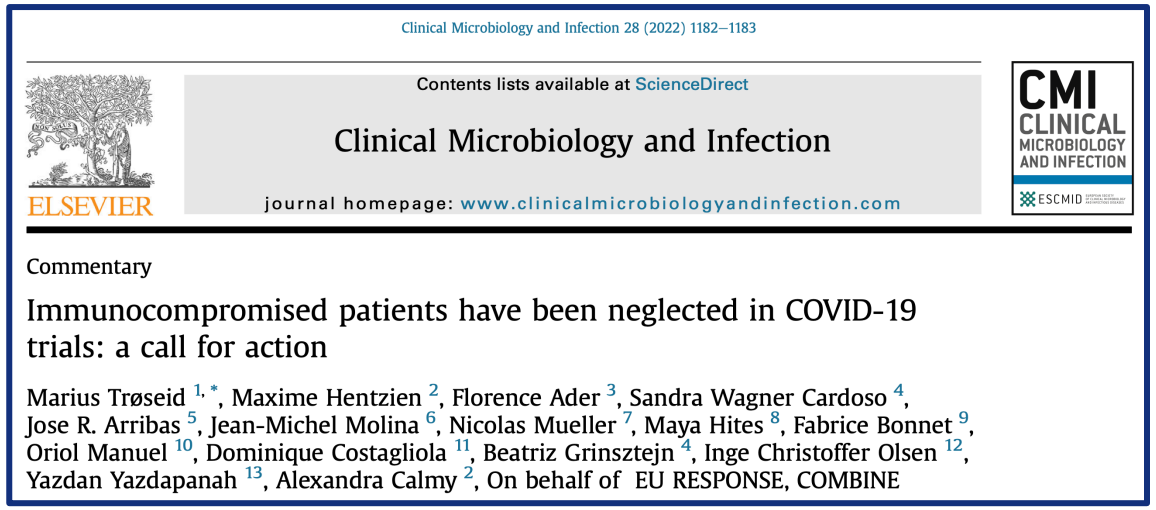
Florence Ader, Maude Bouscambert-Duchamp, Maya Hites, Nathan Peiffer-Smadja, Julien Poissy, Drifa Belhadi, Alpha Diallo, Minh-Patrick Lê, Gilles Peytavin, Thérèse Staub, Richard Greil, Jérémie Guedj, Jose-Artur Paiva, Dominique Costagliola, Yazdan Yazdanpanah, Charles Burdet, France Mentré*, and the DisCoVeRy Study Group*

Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials

Alain Amstutz, Benjamin Speich*, France Mentré, Corina Silvia Rueegg, Drifa Belhadi, Lambert Assoumou, Charles Burdet, Srinivas Murthy, Lori Elizabeth Dodd, Yeming Wang, Kari A O Tikkinen, Florence Ader, Maya Hites, Maude Bouscambert, Mary Anne Trabaud, Mike Fralick, Todd C Lee, Ruxandra Pinto, Andreas Barratt-Due, Fridtjof Lund-Johansen, Fredrik Müller, Olli P O Nevalainen, Bin Cao, Tyler Bonnett, Alexandra Griessbach, Ala Taji Heravi, Christof Schönenberger, Perrine Janiaud, Laura Werlen, Soheila Aghlmandi, Stefan Schandelmaier, Yazdan Yazdanpanah, Dominique Costagliola, Inge Christoffer Olsen, Matthias Briel*

Scientific Findings/ Therapeutic Guidance

Advocacy



Clinical Microbiology and Infection 28 (2022) 1182–1183

Contents lists available at ScienceDirect

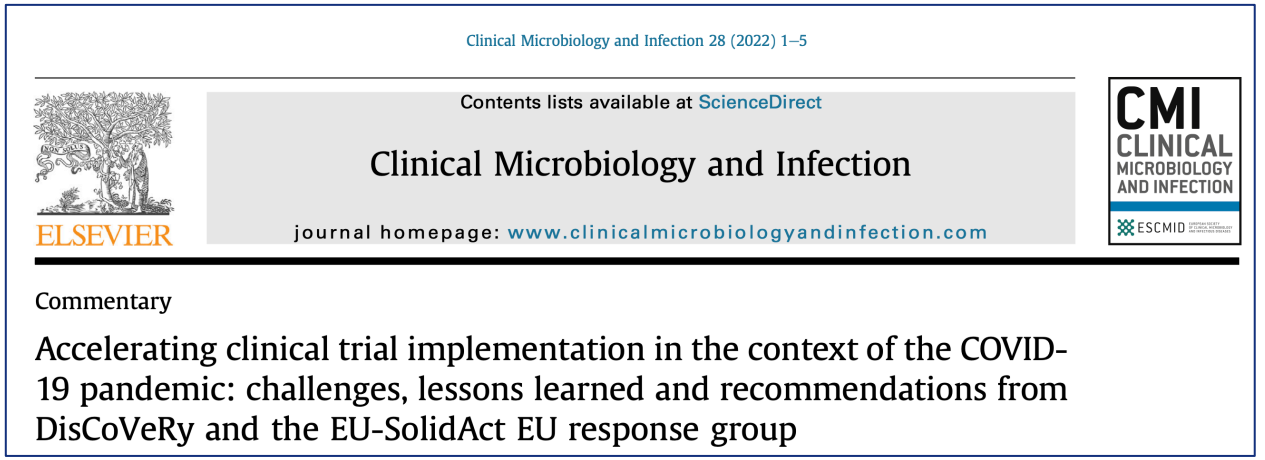
Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

Immunocompromised patients have been neglected in COVID-19 trials: a call for action

Marius Trøseid [1, *], Maxime Hentzien [2], Florence Ader [3], Sandra Wagner Cardoso [4], Jose R. Arribas [5], Jean-Michel Molina [6], Nicolas Mueller [7], Maya Hites [8], Fabrice Bonnet [9], Oriol Manuel [10], Dominique Costagliola [11], Beatriz Grinsztejn [4], Inge Christoffer Olsen [12], Yazdan Yazdapanah [13], Alexandra Calmy [2], On behalf of EU RESPONSE, COMBINE



Clinical Microbiology and Infection 28 (2022) 1–5

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Commentary

Accelerating clinical trial implementation in the context of the COVID-19 pandemic: challenges, lessons learned and recommendations from DisCoVeRy and the EU-SolidAct EU response group

Reflexions on structure/ functioning of trials during a pandemic

DOI: 10.1002/prp2.1072

REVIEW

Management of pharmacovigilance during the COVID-19 pandemic crisis by the safety department of an academic sponsor: Lessons learnt and challenges from the EU DisCoVeRy clinical trial

Contemporary Clinical Trials 131 (2023) 107267

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

Ensuring quality control in a COVID-19 clinical trial during the pandemic: The experience of the Inserm C20–15 DisCoVeRy study

Claire Fougerou-Leurent [a,*], Christelle Delmas [b], Juliette Saillard [c], Marina Dumousseaux [b], Assia Ferrane [b], Noémie Mercier [c], Vida Terzic [c], Soizic Le Mestre [c], Aline Dechanet [d], Drifa Belhadi [d], Annabelle Metois [d], Charles Burdet [d], France Mentré [d], Marion Noret [e], Alpha Diallo [c], Ventzislava Petrov-Sanchez [c], Sandrine Couffin-Cadiergues [b], Maya Hites [f], Florence Ader [g,h], Hélène Esperou [b]

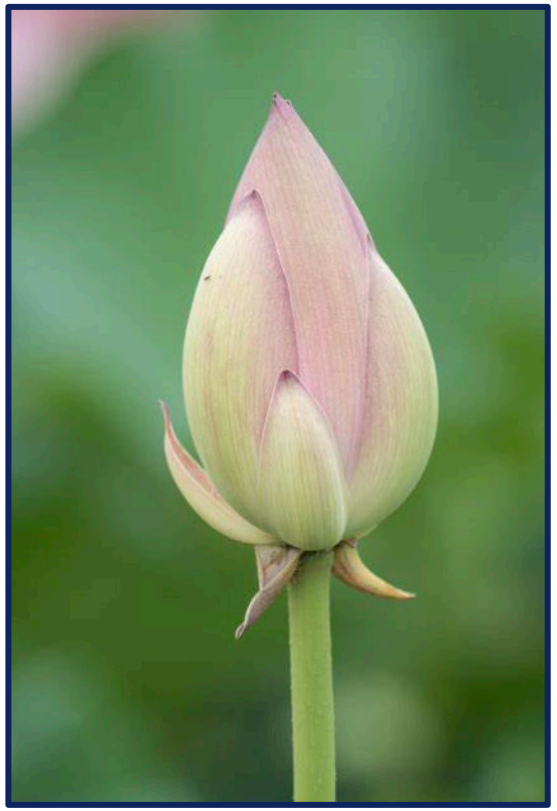
REVIEW ARTICLE

Implementation of a centralized pharmacovigilance system in academic pan-European clinical trials: Experience from EU-Response and conect4children consortia

Vida Terzić [1,2] | Léa Levoyer [1,2] | Mélanie Figarella [1,2] | Elisabetta Bigagli [3,4] | Noémie Mercier [1,2] | Lucie De Gastines [1,2] | Séverine Gibowski [1,2] | Marius Trøseid [5] | Jacques Demotes [6] | Inge Christoffer Olsen [7] | Maya Hites [8] | Florence Ader [9] | José Ramón Arribas Lopez [10] | France Mentré [11] | Hélène Espérou [12] | Dominique Costagliola [13] | John-Arne Røttingen [14] | Julien Poissy [15] | Jean-Christophe Rozé [16] | Adilia Warris [17] | Jackie O'Leary [18] | Ricardo M. Fernandes [19] | Lambert Assoumou [13] | Regis Hankard [20] | Mark A. Turner [21,22] | Yazdan Yazdanpanah [1,2,23] | Alpha Diallo [1,2] | EU-Response safety group | c4c safety group

Subject		Hypotheses/ Explorations proposed
1. Identifying circulating biomarkers of interest and respiratory microbiota signatures		
	Exploring the predictive value of circulating biomarkers of vascular and fibrosis dysfunction in patients hospitalized with COVID-19	sST2 kinetics may be tightly associated with clinical outcome. To address the hypothesis, we will assess its plasma kinetics at various time-points (days 3, 5, 8, 11, 29) and study its association to key prognosis criteria such as the National Early Warning Score (NEWS-2 score) and the ISARIC 4C score
	Exploring the link between antigenemia and interferon response deregulation in patients hospitalized with COVID-19	Circulating N-antigenemia may be a key immunogenic factor contributing to extra-pulmonary disease and endothelial and tissue damages
	Assessing respiratory microbiota signatures associated with COVID-19 outcome	Metagenomic sequencing on nasal swabs from COVID-19 cohorts within EU-RESPONSE and collaborative European influenza cohorts. State-of-the-art bioinformatics will be used to define disease-related respiratory microbiome signatures associated with host immunity, immunomodulating treatment, superinfections, and clinical outcomes.
2. Bridging the gap between the biomarkers of severity and disease complications		
	Bacterial superinfections in critically ill patients	COVID-19 patients with alteration of immune response and immune-induced coagulopathy and endotheliopathy would be at higher risk for developing ventilator-aquired pneumonia (VAP) of bacterial origin
	Fungal superinfections in critically ill patients	COVID-19 patients with alteration of immune response and immune-induced coagulopathy and endotheliopathy would be at higher risk for developing invasive fungal infections (IFI), notably COVID-19-associated pulmonary aspergillosis (CAPA)
3. Investigating SARS-CoV-2 within-host diversity under remdesivir treatment and point-of-care tests for neutralization assays		
	SARS-CoV-2 within-host diversity under remdesivir treatment	Does remdesivir exert selective pressure in-vivo which could promote emergence of SARS-CoV2 variants?
	Point-of-care tests for real-time neutralization assays	allow to finalize the development of new routine methods to quantify neutralizing antibodies, whether in the setting of post-disease, post-vaccine, or post-monoclonal antibody administration

Collateral benefits



Creation of a European network of virology reference laboratories: VIRvOLT (Virology Operational Labs for Drug Testing)

Austria, Belgium, Czech Republic, France, Greece, Hungary, Luxemburg, Poland, Portugal, Slovakia

Objectives

- Harmonization of procedures, techniques and capacity building for virological analyses
- Comparable results in a short time with the setting up of normalized viral loads in respiratory samples
- **Preparedness and reactivity in case of a new viral emergence**

To date

- ✓ **10 laboratories trained by bioMérieux and tests carried out** by the labs, on their platform, using the same panel
- ✓ **8 laboratories validated** (Belgium under validation, Withdrawal of Norway, Austria validated but withdrawal after validation)
- ✓ 7 laboratories performed an **EQA in April 2023**

Achievements

- ✓ A European network of laboratories capable of providing virological **data in a short time** during therapeutic trials, in Europe, on different viruses, known or emerging.
- ✓ Utilisation of the same technique across laboratories to guarantee **reliable and comparable results** (normalized viral loads) at a European scale
- ✓ **Partnership with Industry, bioMérieux**, known for their skills in developing quantitative PCR kits and recognized internationally to be capable of adapting an existing molecular kit to target an emerging pathogen with pandemic potential in a short time.

And… in the meantime.. we want to keep on running!!!

Transition to a permanent structure

- EU-RESPONSE:
  - Focus on hospitalisations, network of hospitals
  - COVID-19 no longer is a major concern in this population
  - How to turn a clinical network of 100+ sites in 17+ countries into a more permanent structure?
  - How to keep the operational/methodological and laboratory networks alive?

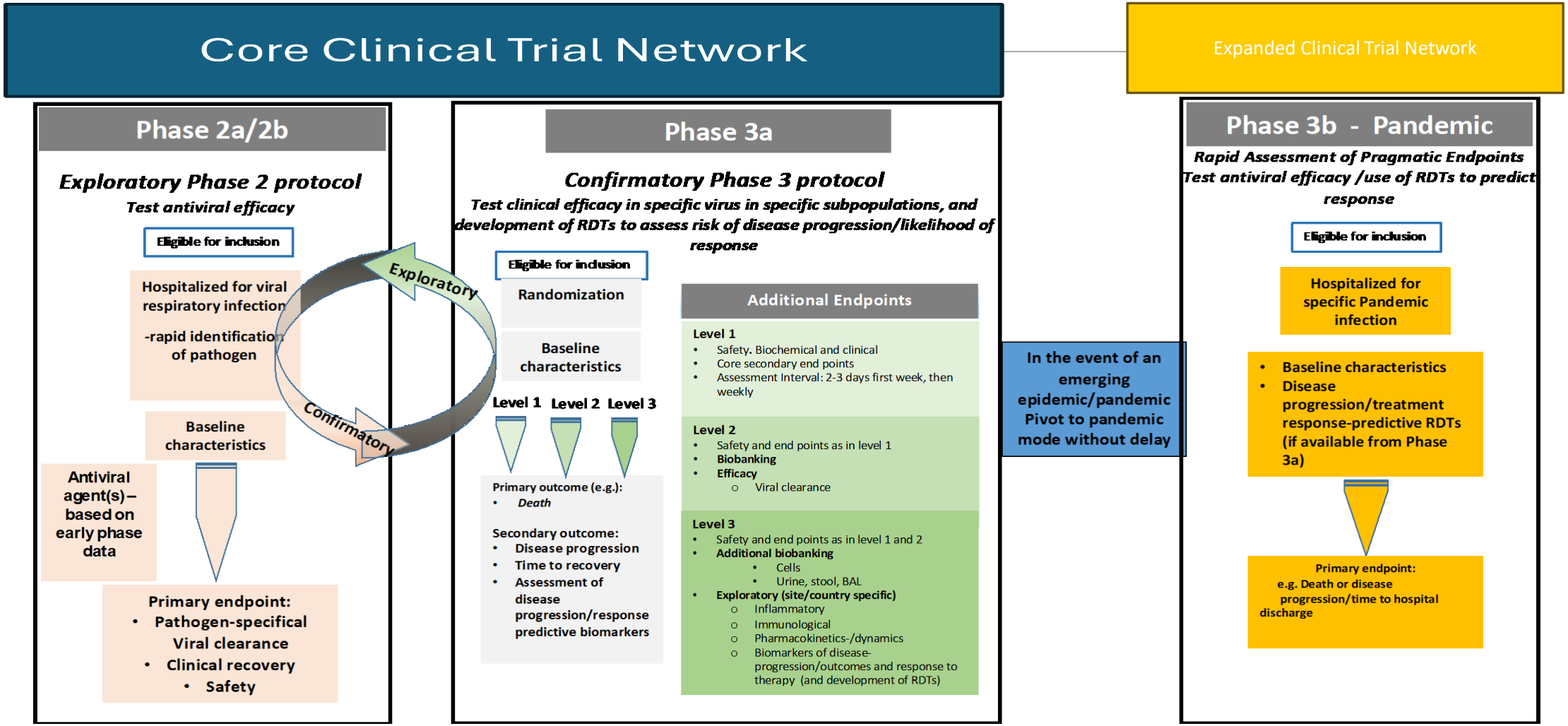
Challenges

- What kind of network do we want/need?
  - Warm-based or cold-based
  - Pulmonary infectious diseases or general (what is general?)
  - Focus on **repurposing** or **novel drugs** or **both**
  - How flexible should it be?
    - Some sites/hospitals/countries only had ID wards or intensive care units in EU-RESPONSE. Do we need both in all countries?
  - **Phase 2** or **phase 3** or **both**?

Syndromic approach

- **Target population:** Patients hospitalised due to general viral respiratory tract infections
- **Intervention:** broad-spectrum anti-viral
- **Control:** Placebo and/or Standard of Care
- **Outcome:** Viral / clinical

EU-ProAct


Core Clinical Trial Network
Expanded Clinical Trial Network
Phase 2a/2b
Exploratory Phase 2 protocol
Test antiviral efficacy
Eligible for inclusion
Hospitalized for viral respiratory infection
-rapid identification of pathogen
Baseline characteristics
Antiviral agent(s)– based on early phase data
Primary endpoint:
• Pathogen-specifical Viral clearance
• Clinical recovery
• Safety
Exploratory
Confirmatory
Phase 3a
Confirmatory Phase 3 protocol
Test clinical efficacy in specific virus in specific subpopulations, and development of RDTs to assess risk of disease progression/likelihood of response
Eligible for inclusion
Randomization
Baseline characteristics
Level 1 Level 2 Level 3
Primary outcome (e.g.):
• Death
Secondary outcome:
• Disease progression
• Time to recovery
• Assessment of disease progression/response predictive biomarkers
Additional Endpoints
Level 1
• Safety. Biochemical and clinical
• Core secondary end points
• Assessment Interval: 2-3 days first week, then weekly
Level 2
• Safety and end points as in level 1
• Biobanking
• Efficacy
o Viral clearance
Level 3
• Safety and end points as in level 1 and 2
• Additional biobanking
• Cells
• Urine, stool, BAL
• Exploratory (site/country specific)
o Inflammatory
o Immunological
o Pharmacokinetics-/dynamics
o Biomarkers of disease-progression/outcomes and response to therapy (and development of RDTs)
In the event of an emerging epidemic/pandemic Pivot to pandemic mode without delay
Phase 3b - Pandemic
Rapid Assessment of Pragmatic Endpoints
Test antiviral efficacy /use of RDTs to predict response
Eligible for inclusion
Hospitalized for specific Pandemic infection
• Baseline characteristics
• Disease progression/treatment response-predictive RDTs (if available from Phase 3a)
Primary endpoint:
e.g. Death or disease progression/time to hospital discharge

Discussion

- Pros:
  - Warm-based
  - easy to pivot into outbreak mode
  - Clinically relevant question (which antiviral to use)
- Cons:
  - Restricted to viral respiratory tract infections
  - Initially only 30-40 sites in Phase 2, what about the rest? Cold-based?

Conclusions

- EU-RESPONSE has done a lot of running.. And we hope to continue doing so!

- A European clinical trials + virology network has been created

- Significant useful scientific knowledge has been obtained

- Master clinical trial protocols have been created for future epidemic/pandemic outbreaks with varied levels of participation

- Significant thought has been put into how best to move forward:
  - Syndromic approach
  - Pre-validated contract templates for all European sites