Fondazione Regionale per la Ricerca Biomedica

DECRETO NR. 124 del 15/11/2024

OGGETTO: BANDO EJP RD JOINT TRANSNATIONAL CALL FOR PROPOSALS 2022 — EROGAZIONE IN FAVORE DELLA FONDAZIONE IRCCS POLICLINICO SAN MATTEO, PARTNER NR. 1 DEL PROGETTO ACRONIMO EUREKA (EJPRD22-169) DI UNA RATA PARI A **€ 11.447,41** (CUP B13C23001650002)

L'atto si compone di 20 pagine
di cui 16 pagine di allegati

Fondazione Regionale per la Ricerca Biomedica

IL DIRETTORE GENERALE DELLA FONDAZIONE REGIONALE PER LA RICERCA BIOMEDICA

PREMESSO CHE:

- la Fondazione IRCCS Policlinico San Matteo (di seguito "*Beneficiario*"), Coordinatore del progetto transnazionale dal titolo "Bonding molecular genotyping and phenotyping to outcome measures in AL amyloidosis: A EUropean REgistry and sample sharing networK to promote the diagnosis and management of light chain Amyloidosis" (EJPRD22-169 Acronimo EUREKA), Responsabile scientifico Dott. Giovanni Palladini, è risultata ammessa a finanziamento in risposta al programma europeo EJP RD, Bando JTC 2022 per un importo complessivo assegnato pari a € 300.000,00;
- il Beneficiario ha inviato a FRRB, in data 23.12.2022 (PEC Prot. nr. 20220507E), la "*Dichiarazione di svolgimento di attività non economica ai sensi delle norme in materia di aiuti di Stato*" e la "*Dichiarazione di accettazione del contributo*";

CONSIDERATO CHE:

- il progetto Acronimo EUREKA ha avuto avvio in data 01.06.2023 per una durata di 36 mesi, come comunicato dal Responsabile Scientifico il 28.04.2023 (PEC Prot. nr. 20230111E) e riportato nella Convenzione stipulata tra FRRB e il Beneficiario;
- ai sensi dell'Art. 8.1 (Erogazione del contributo) della Convenzione sopracitata, l'erogazione al Beneficiario sarà effettuata da FRRB secondo le seguenti modalità:
  - "*due tranche successive entro 60 giorni dalla presentazione della prima e della seconda rendicontazione annuale, previa accettazione della documentazione ricevuta da parte di FRRB. L'importo del contributo sarà calcolato in base ai costi eleggibili effettivamente rendicontati da ciascun Beneficiario.*";

DATO ATTO CHE:

- FRRB ha erogato, con Decreto del Direttore Generale di FRRB nr. 35 del 15.06.2023, la quota di anticipo pari al 30% del contributo totale assegnato al Beneficiario, per un importo pari a € 90.000,00;
- al termine della prima annualità i costi eleggibili ammontavano a € 101.447,41 e, a fronte dell'erogazione a titolo di anticipo è stato possibile richiedere una erogazione pari a € 11.447,41;
- in data 24.10.2024, FRRB ha comunicato al Beneficiario (PEC Prot. nr. 20240266E) l'esito positivo dell'istruttoria di verifica della rendicontazione economica richiedendo, al

contempo, l'invio della richiesta di erogazione;

PRESO ATTO che il Responsabile dell'Area Amministrativa, Dr. Marco Trincavelli, ha verificato che lo stanziamento di € 11.447,41 è finanziariamente sostenibile al capitolo di spesa 20.15.5043, rientrante nei bandi previsti nel Piano di Azione FRRB relativo all'esercizio 2021, approvato da Regione Lombardia con DGR n. XI/5341 del 04/10/2021 e incassato da FRRB in data 22/11/2021;

VERIFICATA la regolarità contributiva del Beneficiario tramite acquisizione d'ufficio del DURC da parte di FRRB (Allegato 4);

RICHIAMATI:

- la DGR nr. IX/2401 del 26.10.2011 con la quale Regione Lombardia ha costituito la "Fondazione Regionale per la Ricerca Biomedica" (di seguito *"FRRB"),* il cui scopo statutario è quello di promuovere la ricerca scientifica e sanitaria nel settore delle Scienze della Vita;
- la DGR n. XII/1670 del 28.12.2023 con la quale è stato approvato lo schema di Accordo di collaborazione tra FRRB e Regione Lombardia;
- la DGR nr. XI /5341 del 004.10.2021 con la quale è stato approvato il Piano di Azione 2021 che prevede, al suo interno, l'allocazione fino ad un massimo di € 1.500.000,00 per la partecipazione di FRRB programma europeo European Joint Programme on Rare on Diseases (EJP RD) Bando JTC 2022;
- la DGR n. XI/5786 del 21.12.2021 con la quale è stato approvato il nuovo Statuto di FRRB;

VISTI:

- il Regolamento (UE) nr. 1291/2013 del Parlamento Europeo e del Consiglio dell'11.12.2013 che istituisce il Programma Quadro di Ricerca e Innovazione (2014-2020) "*Horizon 2020*" quale strumento di finanziamento della ricerca scientifica e dell'innovazione per progetti di ricerca o azioni volte all'innovazione scientifica e tecnologica che portino un significativo impatto sulla vita dei cittadini europei;
- il Grant Agreement nr. 825575 partito il 01.01.2019, con l'obiettivo di supportare e coordinare gli sforzi nel campo della ricerca di Stati membri, associati e Paesi extra-europei, nel campo delle malattie rare, anche al fine di implementare gli obiettivi dell'International Rare Disease Research Consortium (IRDiRC);
- la Comunicazione della Commissione Europea nr. 2014/C 198/01 "Disciplina degli aiuti di Stato a favore di ricerca, sviluppo e innovazione" e ss.mm.ii;
- il Regolamento UE nr. 2021/1237 della Commissione del 23.07.2021 che ha modificato il

Fondazione Regionale per la Ricerca Biomedica

Regolamento UE nr. 651/2014 che dichiara alcune categorie di aiuti compatibili con il mercato interno in applicazione degli articoli 107 e 108 del Trattato;

- la scheda di rendicontazione economica (*Financial report*) contenente il dettaglio dei costi sostenuti dal Beneficiario nel corso del primo anno di attività pari a € 101.447,41 *(Reporting period 01/06/2023 – 31/05/2024)* (Allegato 1);
- la richiesta di erogazione pervenuta in data 09.11.2024 per un importo complessivo pari a € 11.447,41 (Allegato 2);
- il Codice Unico di Progetto (CUP) B13C23001650002, generato dal Beneficiario in fase di avvio del progetto;
- il report scientifico (Allegato 3);

DECRETA

per i motivi espressi in premessa, parte integrante del presente provvedimento:

1. di autorizzare l'erogazione in favore della Fondazione IRCCS Policlinico San Matteo, con sede legale in Pavia, Str. Campeggi, della rata di pagamento pari a € 11.447,41, in relazione al progetto EUREKA, Responsabile Scientifico Dott. Giovanni Palladini (CUP B13C23001650002);
2. di provvedere alla pubblicazione del presente Decreto sul sito web di FRRB, a cura del Responsabile del procedimento ai sensi della Legge 241/1990, Dott.ssa Giulia Maria Rossignolo.

IL DIRETTORE GENERALE
Veronica Comi

Veronica
Comi
15.11.2024
17:52:30
GMT+02:00

Fondazione Regionale per la Ricerca Biomedica

COST STATEMENT

Rev.0 del 31/10/2022

EU PROJECT (please select)	EJP RD		
JTC	2022		
PROJECT ID	EJPRD22-169		
PROJECT TITLE AND ACRONYM	Bonding molecular genotyping and phenotyping to outcome measures in AL amyloidosis: A EUropean REgistry and sample sharing networK to promote the diagnosis and managementof light chain Amyloidosis - EUREKA		
LOMBARDY BENEFICIARY	Fondazione IRCCS Policlinico San Matteo		
NAME OF PRINCIPAL INVESTIGATOR	Prof. Giovanni Palladini		
CUP NUMBER	B13C23001650002		
REPORTING PERIOD (FROM-TO)	01/06/2023 - 31/05/2024	YEAR (please select)	1
IS VAT RECOVERABLE? (YES/NO)	NO		

COST CATEGORIES	TOTAL BUDGET	REPORTING PERIOD 1	REPORTING PERIOD 2	REPORTING PERIOD 3	TOTAL COST STATEMENT	DEVIATION FROM ORIGINAL BUDGET
TOTAL PERSONNEL COSTS	*€ 120.000,00*	*€ 32.666,67*			€ 32.666,67	€ 87.333,33
CONSUMABLES	*€ 94.000,00*	*€ 48.148,72*			€ 48.148,72	€ 45.851,28
EQUIPMENT (LEASING OR ON HIRE)	*€ 0,00*	*€ 0,00*			€ 0,00	€ 0,00
TRAVEL & ACCOMODATION	*€ 10.000,00*	*€ 275,25*			€ 275,25	€ 9.724,75
PUBLICATIONS	*€ 6.000,00*	*€ 0,00*			€ 0,00	€ 6.000,00
OTHER DIRECT COSTS	*€ 4.000,00*	*€ 0,00*			€ 0,00	€ 4.000,00
SUBTOTAL	**€ 234.000,00**	**€ 81.090,64**	**€ 0,00**	**€ 0,00**	**€ 81.090,64**	€ 152.909,36
OVERHEADS	*€ 46.800,00*	*€ 16.218,13*	*€ 0,00*	*€ 0,00*	*€ 16.218,13*	€ 30.581,87
SUBCONTRACTING COSTS	*€ 19.200,00*	*€ 4.138,64*	*€ 0,00*	*€ 0,00*	*€ 4.138,64*	€ 15.061,36
TOTAL REQUESTED BUDGET	**€ 300.000,00**	**€ 101.447,41**	**€ 0,00**	**€ 0,00**	**€ 101.447,41**	**€ 198.552,59**

PERSONNEL COSTS

Please refer to the JTC guidelines for the eligibility of personnel costs

NAME	POSITION	CONTRACT TYPE	PERIOD (FROM - TO)	EURO AMOUNT
Mazzini Giulia	Biotecnologo	Prestazione Professionale	01/11/23 - 30/04/25	18.666,69
Corpina Chiara	Biologo	Prestazione Professionale	01/12/23 - 30/11/24	14.000,00
			TOTAL € AMOUNT	**32.666,69**

CONSUMABLES

Please refer to the JTC guidelines for the eligibility of costs

NAME	ITEM DESCRIPTION	INVOICE NR.	INVOICE DATE	PAYMENT DATE	EURO AMOUNT
CAMPOVERDE s.r.l.	Materiali diagnostici	FT - 1552 E1	03/10/23	23/11/2023	1.043,83
BECTON DICKINSON ITALIA SPA	Materiali diagnostici	FT - 232067592	03/11/23	27/12/2023	2.982,17
LIFE TECHNOLOGIES IT. (FIL.L.T. EU)	Materiali diagnostici	FT - 23064982	07/11/23	27/11/2023	4.923,14
FISHER SCIENTIFIC SAS	Materiali diagnostici	FT - 4180153570	09/11/23	27/12/2023	388,57
LABOSPACE SRL	Materiali diagnostici	FT - 187/E	16/11/23	19/12/2023	563,64
EUROCLONE S.P.A.	Materiali diagnostici	FT - 9937/SP	17/11/23	27/12/2023	1.721,12
BECKMAN COULTER SRL	Materiali diagnostici	FT - 2023057673	07/12/23	27/12/2023	163,85
BECKMAN COULTER SRL	Materiali diagnostici	FT - 2023059260	15/12/23	16/01/2024	2,81
BECKMAN COULTER SRL	Materiali diagnostici	FT - 2023059466	18/12/23	16/01/2024	5,61
QIAGEN s.r.l.	Materiali diagnostici	FT - 0980303591	18/12/23	27/02/2024	2.244,31
LIFE TECHNOLOGIES IT. (FIL.L.T. EU)	Materiali diagnostici	FT - 23076759	19/12/23	07/02/2024	2.708,18
CARLO ERBA REAGENTS SRL	Reagenti	FT - 2123051477	20/12/23	05/03/2024	724,07
MILTENYI BIOTEC S.R.L.	Reagenti	FT - 1022305485	20/12/23	28/02/2024	3.515,43
MILTENYI BIOTEC S.R.L.	Reagenti	FT - 1022305452	20/12/23	27/02/2024	1.257,21
VWR INTERNATIONAL SRL	Reagenti	FT - 3074023714	21/12/23	30/01/2024	219,72
LIFE TECHNOLOGIES IT. (FIL.L.T. EU)	Materiali diagnostici	FT - 24000224	02/01/24	07/02/2024	1.739,23
BIOSIGMA SPA	Reagenti	FT - 24FS000970	23/01/24	28/02/2024	165,92
QIAGEN s.r.l.	Materiali diagnostici	FT - 0980304850	25/01/24	27/02/2024	2.434,96
BIOSIGMA SPA	Reagenti	FT - 24FS001315	26/01/24	28/02/2024	199,50
BECTON DICKINSON ITALIA SPA	Materiali diagnostici	FT - 242007979	05/02/24	26/02/2024	2.982,17
ILLUMINA ITALY S.R.L.	Materiali diagnostici	FT - 7080045486	08/02/24	22/03/2024	2.466,17
EUROCLONE S.P.A.	Materiali diagnostici	FT - 920/SP	09/02/24	04/03/2024	2.934,71
BIOSIGMA SPA	Reagenti	FT - 24FS002243	12/02/24	25/03/2024	244,00
BECTON DICKINSON ITALIA SPA	Materiali diagnostici	FT - 242010194	13/02/24	22/03/2024	456,28
CARLO ERBA REAGENTS SRL	Reagenti	FT - 2124006915	15/02/24	19/04/2024	131,76
MERCK LIFE SCIENCE SRL	Materiali diagnostici	FT - 8230725471	15/02/24	05/03/2024	189,59
FISHER SCIENTIFIC SAS	Materiali diagnostici	FT - 4180160580	15/02/24	02/04/2024	2.888,55
FISHER SCIENTIFIC SAS	Materiali diagnostici	FT - 4180160679	16/02/24	02/04/2024	104,31
LIFE TECHNOLOGIES IT. (FIL.L.T. EU)	Materiali diagnostici	FT - 24012349	28/02/24	18/04/2024	3.497,96
WATERS SPA	Materiali diagnostici	FT - 311045383	05/03/24	15/04/2024	2.260,66
FISHER SCIENTIFIC SAS	Materiali diagnostici	FT - 4180162241	07/03/24	08/05/2024	638,41
FISHER SCIENTIFIC SAS	Materiali diagnostici	FT - 4180163384	21/03/24	08/05/2024	501,05
EUROCLONE S.P.A.	Materiali diagnostici	FT - 2713/SP	12/04/24	29/05/2024	1.770,53
BIOSIGMA SPA	Materiali diagnostici	FT - 24FS007115	24/04/24	27/05/2024	79,30
				TOTAL € AMOUNT	**48.148,72**

EQUIPMENT (LEASING OR ON HIRE)

NAME	ITEM DESCRIPTION	INVOICE NR.	INVOICE DATE	EURO AMOUNT	% OF USE OF THE EQUIPMENT FOR PROJECT'S PURPOSES	AMORTISATION MONTHS	EURO AMOUNT
						TOTAL € AMOUNT	0,00

TRAVEL AND ACCOMODATION

Max 10% of direct costs

NAME	REASON FOR TRAVELING	DESTINATION	PERIOD (FROM - TO)	EURO AMOUNT
Mazzini Giulia	partecipazione attiva a 21° PROTEOMIX	Roma	28/11/23 - 29/11/23	275,25
			TOTAL € AMOUNT	275,25

PUBLICATIONS

max 5% of direct costs

NAME	DESCRIPTION	INVOICE NR.	INVOICE DATE	EURO AMOUNT
			TOTAL € AMOUNT	0,00

OTHER DIRECT COSTS

Please refer to the JTC guidelines for the eligibility of costs

NAME	ITEM DESCRIPTION	INVOICE NR.	INVOICE DATE	PAYMENT DATE	EURO AMOUNT
				TOTAL € AMOUNT	0,00

SUBCONTRACTING

Max 20% of direct costs

NAME	PROCEDURE APPLIED	DESCRIPTION (provide details on service duration)	INVOICE NR.	INVOICE DATE	EURO AMOUNT
ETH FUNCTIONAL GENOMICS CENTER ZURICH	ditta scelta per continuità, 3 preventivi valutati precedentemente	servizio di sequenziamento	FT - 1300412107	30/11/23	3.392,33
Pagamento IVA su Fattura estero	F24 - Ente a credito nel mese di Dicembre 2023	pagamento IVA intrastat	FT - 1300412107	31/12/23	746,31
				TOTAL € AMOUNT	**4.138,64**

I declare that all the documentation listed in this table is archived at the Beneficiary premises and available in case of financial audits.

Name of the Beneficiary Legal Representative

Signature of the Beneficiary Legal Representative

Firmato da:
VITTORIO LUCIANO BELLOTTI
Codice fiscale: BLLVTR57B05D150F
Valido da: 17-10-2022 14:26:12 a: 17-10-2025 02:00:00
Certificato emesso da: InfoCert Qualified Electronic Signature CA 3, InfoCert S.p.A., IT
Riferimento temporale 'SigningTime': 19-07-2024 12:06:19
Approvo il documento

Date, Place and Stamp:

Fondazione IRCCS Policlinico San Matteo
Sistema Socio Sanitario
Regione Lombardia

DIREZIONE SCIENTIFICA

Direttore
Vittorio Bellotti

Tel. 0382 503640

direzione.scientifica@smatteo.pv.it

Fasc. 2022-1.1.6/54
Prot. 0059539/24

RICHIESTA EROGAZIONE CONTRIBUTO
DICHIARAZIONE SOSTITUTIVA DI ATTO NOTORIO
(D.P.R. 445/2000)

Spett.le
Fondazione Regionale per la Ricerca Biomedica
Via T. Taramelli, 12
20124 Milano
PEC:
fondazioneregionalericercabiomedica@pec.it

OGGETTO: Richiesta erogazione prima rata
TITOLO PROGETTO: EUREKA - Bonding molecular genotyping and phenotyping to outcome measures in AL amyloidosis: a **EU**ropean **RE**gistry and sample sharing networ**K** to promote the diagnosis and management of light chain **A**myloidosis
RESPONSABILE SCIENTIFICO: Prof. Giovanni Palladini
CODICE CUP: B13C23001650002

Il sottoscritto Vittorio Bellotti nato a [redacted] il [redacted] e residente a [redacted], in qualità di delegato del Legale Rappresentante della Fondazione I.R.C.C.S. Policlinico San Matteo partecipante al progetto in oggetto, con sede legale in comune di Pavia (PV) 27100, Viale Golgi n. 19, CODICE FISCALE 00303490189 - PARTITA IVA 0050580590180
INDIRIZZO E-MAIL protocollo@pec.smatteo.pv.it e grant.office@smatteo.pv.it

CHIEDE

l'erogazione del saldo della prima rata pari a € 11.447,41 (undicimilaquattrocentoquarantasette,41)
Il pagamento dovrà essere effettuato tramite bollettino PagoPA, allegato alla presente comunicazione.

Cordiali saluti,

Pavia, *data della sottoscrizione digitale*

F.to DIGITALMENTE Prof. Vittorio Bellotti
(delegato, ai sensi dell'Art. 24 del DLgs n. 82/2005)

Firmato da:
VITTORIO LUCIANO BELLOTTI
Codice fiscale: BLLVTR57B05D150F
Valido da: 17-10-2022 13:26:12 a: 17-10-2025 01:00:00
Certificato emesso da: InfoCert Qualified Electronic Signature CA 3, InfoCert S.p.A., IT
Riferimento temporale 'SigningTime': 05-11-2024 11:57:40
Approvo il documento

RESPONSABILE DEL PROCEDIMENTO: Dott.ssa Luigia Scudeller - SSD Grant Office, TTO e Servizio Documentazione Scientifica
RESPONSABILE DELL'ISTRUTTORIA: Sig.ra Stefania Zavattoni - SSD Grant Office, TTO e Servizio Documentazione Scientifica

pagoPA AVVISO DI PAGAMENTO

Sistema Socio Sanitario
Regione Lombardia
Fondazione IRCCS Policlinico San Matteo

Documento n. 7000585 del: 04/11/2024

ENTE CREDITORE Cod. Fiscale 00303490189

Fondazione IRCCS Policlinico S. Matteo

Viale Camillo Golgi 19 27100 Pavia (PV)
03825011

DESTINATARIO AVVISO Cod. Fiscale 97608860157

FONDAZIONE REGIONALE PER LA RICERCA

PIAZZA CITTA' DI LOMBARDIA 1
20124
MILANO - IT

QUANTO E QUANDO PAGARE?

11.447,41 Euro entro il **03/01/2025**

Puoi pagare con **una unica rata.**

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RATA UNICA entro il **03/01/2025**

Qui accanto trovi il codice **QR** e il codice interbancario **CBILL** per pagare attraverso il circuito bancario e gli altri canali di pagamento

Destinatario **FONDAZIONE REGIONALE PER LA**
Ente **Fondazione IRCCS Policlinico S.Matteo**
Euro **11.447,41**
Oggetto del pagamento **Documento n. 7000585 del: 04/11/2024**

CBILL **67E79**
Codice Avviso **3010 0000 0003 2568 61**
Cod. Fiscale Ente Creditore **00303490189**

Bonding molecular genotyping and phenotyping to outcome measures in AL amyloidosis: A EUropean REgistry and sample sharing networK to promote the diagnosis and management of light chain Amyloidosis

Scientific Report

1. State of the art of the project and field

Systemic immunoglobulin light chain (AL) amyloidosis is a severe protein conformational disease caused by misfolding and extracellular deposition of patients (pts)-specific monoclonal light chains (LCs) in form of amyloid fibrils. This process can affect virtually any organ and result in cell death, subversion of tissue architecture, organ dysfunction and eventually death.

The presence of a detectable monoclonal component (M protein) predates the onset of symptomatic amyloid organ involvement by several years and about 95% of pts have an altered free light chain ratio (FLCR) at diagnosis, thus indicating the presence of a monoclonal gammopathy with altered FLCR as a risk factor for the development of AL. Yet, AL is often diagnosed late also in pts with known monoclonal gammopathy under hematologic follow-up. A delayed diagnosis currently represents one of the most acutely unmet medical needs in AL, as advanced damage results in severe functional impairment and deterioration of quality of life, limits therapeutic interventions and is associated with a dismal prognosis, with an overall survival of less than 6 months.

More than by the underlying plasma cell clone, the natural history of AL is dictated by the presence, type and severity of amyloid organ involvement. Heart involvement, present in ≈80% of pts, is the main prognostic determinant and the leading cause of death.

Accurate staging systems based on biomarkers of organ dysfunction/damage have been introduced, validated and rapidly entered the clinical practice. Staging systems have been derived using a clinical modelling approach, where candidate predictors are identified *a priori* based on the clinical and scientific knowledge, and then tested with appropriate statistical methods. While this approach has the clear advantage of resulting in simple scoring systems which are generally well received by the medical community and easily employed, it does not take full advantage of the wealth of clinical and biological information available and may not take into account the complex biology behind a clinical phenomenon.

Moreover, the currently available staging systems have been validated for AL pts at diagnosis. Whether they are appropriate for pts all along the disease course, including after one or more lines of therapy, in the present era of novel anti-plasma cell therapies, is presently unknown.

The primary goal of therapy against AL is the rapid elimination of the amyloidogenic FLC precursor. Achievement of this can swiftly ameliorate organ function and extend

survival. Differently from other monoclonal gammopathies, in AL response to therapy is two-folded: the disappearance or elimination of the underlying plasma cell clone – that is the hematologic response – is a prerequisite for improving dysfunction of affected organs – indicated as organ response – which ultimately dictates pts quality of life and survival.

Of note, hematologic and organ responses, while strictly related, do not always go hand in hand. Indeed, there are AL pts with suboptimal hematologic responses and significant levels of amyloidogenic LCs paradoxically accompanied by satisfactorily organ responses, as well as other pts with deep hematologic responses and minimal or undetectable levels of amyloidogenic LCs yet failing to show recovery of organ dysfunction. A striking example of the latter phenomenon is represented by pts fulfilling the criteria of complete hematologic response (undetectable M protein with serum and urine immunofixation and serum FLC assay) who display a small population of aberrant BMPCs (indicated as minimal residual disease, MRD) as detected by next generation flow cytometry (with at least10^{-5} sensitivity). Indeed, recent data indicate that these pts show significantly less frequent cardiac and renal responses compared to pts in complete response without detectable MRD, indicating that MRD persistence can hinder organ function recovery. However, the role of MRD assessment and the best method to be used in this disease is not yet validated in a prospective setting and the potential utility of a liquid biopsy approach for MRD assessment remains unaddressed.

The discrepancies between hematologic response and organ response may well be related to interindividual variability, possibly including the existence of different toxicity thresholds of amyloidogenic LCs, in relation to the patient-specific, unique LC sequence. The sequence-related structural and biophysical determinants of LC amyloidogenicity and toxicity have just started to be investigated based on analysis of a relatively limited number of LCs. The identification of potential sequence-determinants of individual LC toxicity would benefit from analyses of higher numbers of LCs in the context of clinical data on the disease history.

Approximately 35% of pts responding to first line therapy show a hematological relapse and the question of whether, when and how to retreat these pts arises.

2. Aims and scientific approach

In the frame of the EUREKA consortium, we are building a single registry prospectively collecting all new, consecutive cases of AL amyloidosis evaluated at 4 referral Centers across Europe or at their satellite sites, linked to a cross-border biobank and sample sharing network for molecular/phenotypic profiling of pathogenic PCs and LCs. A fifth site supports the consortium with big data analysis and artificial intelligence applied to health.

The scientific aims of the project are the following:

1) <u>Define the impact of molecular profiling on disease phenotype to promote early diagnosis and guide therapeutic choices</u>, including:

- LC sequencing, analysis of N-glycosylation, AI-based prediction of LC amyloidogenicity;
- NGF-based immunophenotyping of clonal BMPCs and CTCs;
- RNA-Seq and low-pass WGS of clonal BMPCs;
- LC amyloidogenicity in 3D heart on a chip model.

Molecular data will be analyzed in relation to baseline characteristics, response, and survival.

2) Describe the natural history of the disease in a real-world setting and in the contemporary era of availability of novel anti-plasma cell agents, including:

- Evaluation of the performance of existing staging systems and response criteria;
- development of novel staging systems and response criteria, through the incorporation of novel molecular/phenotypic data and the use of big data analysis and AI;
- definition of what a clinically relevant relapse is;
- evaluation of pts-reported outcomes (e.g., quality of life).

3) Define of the role of NGF-based MRD assessment and explore the diagnostic performance of novel sensitive molecular assays for MRD detection, including:

- Defining the role of NGF-based MRD assessment in BM and PB (CTCs);
- exploring the role of a liquid biopsy approach for MRD evaluation

The project is structured according to 7 work packages.

3. Results/Achievements (please describe the activities that have been accomplished during the period from the beginning of the project or the last report to fulfill the aims described in the network proposal. For each WP, specify the main results obtained and their relevance. Estimate the current degree of completion of the planned objectives (for each task, the number of patients already included compared to the number that should be included at the end of the project needs to be clearly mentioned). Please structure the report according to the aims. Please include a description of the collaboration with the participating partners. Refer explicitly to common milestones and deliverables achieved during this reporting period. Include description of shared facilities and/or resources within the consortium.):

The project officially started on June 1st. The present interim report refers to the first 10 months of the project.

WP 1 – Enrollment of prospective, therapy-naïve, newly diagnosed AL pts
(Lead: Pavia and Heidelberg; participants: Pavia, Heidelberg, Utrecht and Pamplona)

Task 1.1 – Ethics committee submission (Mo 1-3)
All clinical centers have collaborated to finalize the study protocol and each clinical center has obtained local IRB approval. Local IRB approval took longer than expected due to different local requirements (e.g. at some centers IRB application could not be filed before completion and signature of the Consortium Agreement).
This task has been completed.

Task 1.2 – Harmonization of data collection and laboratory SOPs (Mo 1-3)
All clinical centers have harmonized data and sample collection procedures. Standard operating procedures have been finalized. A RedCap-based registry containing the clinical variables approved by all clinical centers has been established. This task has been completed.

Task 1.3 – Clinical registry of enrolled pts (Mo 2-14 for enrollment; up to Mo 36 for follow up)
Finalization of the Consortium Agreement took longer than expected due to challenges with multinational agreements. Local IRB approval took longer than expected due to different local requirements (e.g. at some centers IRB application could not be filed before completion and signature of the Consortium Agreement). As a result of these factors, beginning of patients' enrollment was delayed based on what was initially planned. Considering the recent IRB approval from a fourth clinical center and the initial lag-phase for patients' recruitment, we expect to substantially increase the pace of patients' enrollment in the coming months.
Importantly, in addition to the planned enrollment of 400 patients with prospectively collected clinical data and biological samples circulated and collected in the frame of the cross-border network of biobanks, which will form the core set of the EUREKA study, the Consortium committed to integrate the EUREKA prospective clinical registry with prospective data from newly diagnosed patients enrolled at the EUREKA participating centers or their satellite centers, as well as from new partners not initially included in the EUREKA project. This set of data from "registry-only" patients, whose number is expected to be significantly higher than the number of patients included in the core set of the EUREKA study, will be instrumental to increase the power of those planned analyses not requiring integration of clinical data with molecular profiling data, as well as to increase the representativeness of the EUREKA study of the real-world, contemporary series of AL patients.
This is an ongoing task (to be completed by Mo 36). Based on current enrollment and considering only patients to be enrolled in the core set of the EUREKA study, that is patients with both registry data and biobanked samples, this task is completed for <20%.

Task 1.4 – Cross-border biobank network of enrolled pts (Mo 2-36)
Collection of diagnostic leftovers and creation of a cross-border biobank network has started along with patients' enrollment. As this task is strictly related to task 1.3, the generation of the cross-border biobank network was delayed based on what was initially planned. Also in this case, considering the recent IRB approval from a fourth clinical center and the initial lag-phase for patients' recruitment, we expect to substantially increase the pace of patients' enrollment in the coming months.
This is an ongoing task (to be completed by Mo 36). Based on current enrollment and considering samples to be collected at diagnosis, this task is completed for <20%.

WP 2 – Clonal LC profiling
(Lead: Pavia and Utrecht; participants: Pavia, Heidelberg, Utrecht, Pamplona and Muttenz)

Task 2.1 – Sequencing of clonal LCs with SMaRT M-Seq in matched BM and PB samples (Mo 2-18)

Collection of mononuclear cells for RNA extraction from matched BM and PB samples has started in Pamplona, in parallel to patients' enrollment at the respective clinical centers.
Pavia has extended the initial liquid biopsy study on matched BM and PB samples in a cohort of 80 MGUS, MM and AL cases, confirming that a clearly dominant clonal LC can be identified in more than 80% of analyzed pts, with a sequence showing 100% identity with respect to the sequence identified in the matched BM sample.
Pavia and Muttenz have performed a benchmarking analysis of bioinformatics tools to analyze immunoglobulin sequences from NGS datasets. Pavia has also performed a benchmarking analysis of currently available bioinformatics tools to predict the N-glycosylation of a given clonal light chain based on its sequence. Collectively, these tools will be instrumental for the next part of this task.
This is an ongoing task (to be completed by Mo 18), with most of experimental activities to be performed in the second part, exploiting the biological samples prospectively collected at the time of enrollment.

Task 2.2 – Prediction of LC amyloidogenicity using machine learning (Mo 12-30)
This task will start at Mo 12 as planned.

Task 2.3 – Heart-on-a-chip studies (Mo 2-24)
Utrecht is optimizing the 3D-heart-on-a-chip model in collaboration with Pavia, which is providing well-characterized, patients-derived amyloidogenic light chains. All clinical centers all collecting diagnostic leftovers from serum/plasma/urine which will be instrumental to validate candidate biomarkers identified through this innovative preclinical model.
This is an ongoing task (to be completed by Mo 24).

WP 3 – Clonal plasma cell molecular profiling
(Lead: Pamplona and Heidelberg; participants: Pavia, Heidelberg, Utrecht, Pamplona and Muttenz)

Task 3.1 – Immunophenotyping of BM and PB clonal plasma cells at diagnosis (Mo 2-15) and at the time of MRD assessment (up to Mo 36)
Immunophenotyping of BM and PB clonal plasma cells at diagnosis has started in Pamplona, in parallel to patients' enrollment at the respective clinical centers.
This is an ongoing task (to be completed by Mo 36). Based on current enrollment and considering samples to be collected at diagnosis, this task is completed for <20%.

Task 3.2 –Transcriptional profiling of sorted, clonal BMPCs at diagnosis (Mo 2-24) and at the time of MRD assessment (up to Mo 36)
Sorting of clonal BMPCs at diagnosis has started in Pamplona, in parallel to patients' enrollment at the respective clinical centers.
This is an ongoing task (to be completed by Mo 36), with most of experimental activities to be performed in the second part, exploiting the biological samples prospectively collected at the time of enrollment, as well as matched samples collected at the time of MRD.

Task 3.3 – Global genomic profiling of sorted, clonal BMPCs (Mo 2-24)
Aliquots for DNA extraction from sorted clonal BMPCs at diagnosis has started in Pamplona, in parallel to patients' enrollment at the respective clinical centers.

This is an ongoing task (to be completed by Mo 24), with most of experimental activities to be performed in the second part, exploiting the biological samples prospectively collected at the time of enrollment.

WP 4 – Staging, prognostication, response and relapse
(Lead: Pavia, Heidelberg and Muttenz; participants: Pavia, Heidelberg, Utrecht, Pamplona and Muttenz)

Task 4.1 – Validation of available staging systems and response criteria on a contemporary, prospective series (Mo 18-36)
This task will start at Mo 18 as planned.

Task 4.2 – Refinement of staging and prognostication criteria incorporating molecular and cellular profiling data and exploiting big data analysis and artificial intelligence (Mo 18-36)
This task will start at Mo 18 as planned.

Task 4.3 – Definition of a clinically meaningful early relapse (Mo 24-36)
This task will start at Mo 24 as planned.

Task 4.4 – Analysis of QoL and other pts-reported outcome measures in the natural history of the disease in a contemporary series of pts. (Mo 18-36)
This task will start at Mo 18 as planned.

WP 5 – MRD studies
(Lead: Pamplona; participants: Pavia, Heidelberg, Utrecht, Pamplona and Muttenz)

Task 5.1 – Definition of the role of MRD persistence within the BM (at 10^{-6} with NGF) and PB (at 10^{-7} with BloodFlow) on a contemporary, prospective series (Mo 9-36)
Considering that no patient enrolled in the study has yet follow up data after therapy and met the eligibility criteria for MRD assessment (complete hematologic response), the beginning of this task will be postponed.

Task 5.2 – Exploring the role of novel, sensitive molecular assays for MRD assessment (Mo 9-36)
Pavia is working on an NGS-based method for MRD assessment.
This is an ongoing task (to be completed by Mo 36), with most of experimental activities to be performed in the second part, exploiting the biological samples collected at the time of MRD assessment, as well as optimized molecular assays currently under development.

WP 6 – Dissemination, Exploitation, Communication
(Pavia, Heidelberg, Utrecht, Pamplona and Muttenz)

The EUREKA study has been registered in the clinicaltrials.gov portal (NCT06205953).

The design of the EUREKA study will be presented at the forthcoming Symposium of the International Society of Amyloidosis, which will be hosted by the Mayo Clinic in Rochester, MN, USA in May 2024.

The EUREKA study has been advertised by members of the EUREKA Consortium in the context of scientific presentations or discussions at congresses, webinars, meetings of scientific societies etc.

Noteworthy, in light of the commitment to integrate the EUREKA prospective clinical registry with prospective data from newly diagnosed patients enrolled at the EUREKA participating centers or their satellite centers, as well as from new partners not initially included in the EUREKA project, the EUREKA Consortium has already received the expression of interest from several partners who are considering to join the prospective EUREKA registry.

Dissemination, exploitation and communication activities will intensify during the second half of the project as more results from the ongoing studies will emerge.

WP 7 – Project Management and Coordination
(Lead: Pavia; participants: Pavia, Heidelberg, Utrecht, Pamplona and Muttenz)

A Consortium Agreement has been finalized. A kickoff meeting was held on May 16th 2023. Regular meetings are held virtually every 3-4 months.

In this first reporting period, the focus of the consortium meetings were legal/administrative issues, as well as harmonization procedures and logistic aspects.

Besides consortium meetings with all scientific partners, more restricted meetings with a subset of the partners focusing on specific scientific aspects are also regularly held. Such meetings will intensify during the second half of the project as more results from the ongoing studies will emerge.

Shared facilities and/or resources within the consortium

Pavia:
Clinical center and local biobank, immunoglobulin sequencing, mass spectrometry

Heidelberg:
Clinical center and local biobank, low pass whole genome sequencing

Pamplona:
Clinical center and local biobank, next-generation flow cytometry, RNA sequencing

Utrecht:
Clinical center and local biobank, 3D-heart-on-a-chip

Muttenz:
Big data analysis, artificial intelligence, antibody repertoire analysis

4. Discussion

We are building a large, multicenter, international, prospective registry of patients with AL amyloidosis with a linked cross-border biobank network enabling integration of

clinical and innovative molecular profiling data, as well as the application of artificial intelligence and big data analysis. Besides deepening our current understanding of the biology of AL amyloidosis, the data produced within this study will be instrumental in promoting early diagnosis, personalizing individual patient management and in the design of future clinical trials.

The main obstacle encountered so far was related to the bureaucratic and logistic complexity of fulfilling all legal and ethics requirement, finalize the Consortium Agreement, obtain local IRB approval at all clinical centers and start patients' enrollment. Enrollment schedule is delayed based on what was initially projected. However, considering that all clinical centers are now actively recruiting and that the initial lag-phase for patients' recruitment at the largest clinical centers is over, we expect to substantially increase the pace of patients' enrollment in the coming months. It is foreseeable that and extension of the study period will suffice to buffer this initial delay.

A major achievement of the Consortium in this first reporting period was its commitment to integrate the EUREKA prospective clinical registry with prospective data from newly diagnosed patients enrolled at the EUREKA participating centers or their satellite centers, as well as from new partners not initially included in the EUREKA project. This set of data from "registry-only" patients, whose number is expected to be significantly higher than the number of patients included in the core set of the EUREKA study, will be instrumental to increase the power of those planned analyses not requiring integration of clinical data with molecular profiling data, as well as to increase the representativeness of the EUREKA study of the real-world, contemporary series of AL patients.

5. Ethics and legal aspects

Not applicable.

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Codice fiscale	00303490189
Sede legale	VIALE CAMILLO GOLGI 19 PAVIA PV 27100

Con il presente Documento si dichiara che il soggetto sopra identificato RISULTA REGOLARE nei confronti di

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Il Documento ha validità di 120 giorni dalla data della richiesta e si riferisce alla risultanza, alla stessa data, dell'interrogazione degli archivi dell'INPS, dell'INAIL e della CNCE per le imprese che svolgono attività dell'edilizia.