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25 FEB. 2015

AGREEMENT LOCAL HEALTH TRUST NO. 8

CLINICAL STUDY AGREEMENT

Between

Local Health Trust N. 8 of Cagliari (Local Health Trust, hereinafter referred to as "**Trust**"), Tax Code and VAT No. 02261430926, based in Selargius (Su Planu), Via Piero della Francesca, 1 in the person of its Special Commissioner, Dr. Savina Ortu

AND

Celgene Corporation, having its principal office at 86 Morris Avenue, Summit, NJ 07901, USA (hereinafter the "**Company**") represented for the purposes of this Agreement by **Celgene International S.à.r.l**, a limited liability company organized under the laws of Switzerland having its principal office at Route de Perreux, 2017 Boudry, Switzerland represented by Isabelle Coudert.

Whereas

- The Company conducts business in the development of therapeutic products, compounds, and reagents;
- The Trust has acquired expertise in conducting clinical research studies, and laboratory test evaluations and has established and maintains facilities for performing such activities.
- PPD Global Limited with address at Granta Park, Great Abington, Cambridge, United Kingdom, CB21 6GQ acting through its affiliate PPD Italy s.r.l., trading as PPD, having its place of business at Palazzo Verrocchio Centro Direzionale Milano Due, 20090 Segrate (Milan), Italy, Tax code 02303270124, VAT No. 12349730155 and number of registration at the Registry of Enterprises of Milan No. 87210/1998 (hereinafter "PPD" or "CRO") is a clinical research organization principally engaged in the design, set-up and management of human clinical trials, and other related services, on behalf of the manufactures of pharmaceutical products.
- The Company has selected CRO to assist in the management and monitoring of the study more specifically set forth herein and has delegated and authorised CRO to act on its behalf relative to the management of the Study (as defined below).

- the Company is interested in carrying out a clinical trial titled

"A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO COMPARE EFFICACY AND SAFETY OF ORAL AZACITIDINE PLUS BEST SUPPORTIVE CARE VERSUS BEST SUPPORTIVE CARE AS MAINTENANCE THERAPY IN SUBJECTS WITH ACUTE MYLOID LEUKEMIA IN COMPLETE REMISSION" Protocol No. AZA-MDS-003 (hereinafter, respectively, the TRIAL and the Protocol). All Parties agree that the Protocol form part to this Agreement although it may not be included as an Annex to it

- the Company has requested the Trust for the relevant authorisation to carry out the aforementioned clinical-pharmaceutical study, and has appointed as investigator Prof. Emanuele Angelucci working at U.O. Ematologia e CTMO Ospedale Oncologico A. Businco of Cagliari;
- the Company has paid € 3,002.00+ VAT as administration fees for the evaluation of the study:
- during the meeting on 28/01/15, by minute 2.18, the Ethics Committee of the Local Health Trust N. 8 has given its approval for the above trial to be carried out;
- that the COMPANY has signed an appropriate insurance policy with no. ITCANP01345 with the company ACE European Group Limited, to cover the civil liability for the TRIAL pursuant to Art. 3 paragraph 1. f) of Legislative Decree 211/2003;
- the current provisions governing clinical trials with specific reference to Ministerial Decree of 15/07/1997 are hereby acknowledged, and it is therefore agreed that a agreement will be drawn up in order to regulate legal and financial relations;

the following is hereby agreed and stipulated

Art. 1

The recitals and any annexed documents are an integral part of this document.

Art. 2

In accordance with the law, the Trust authorises Prof. Emanuele Angelucci, Head of U.O. Ematologia e CTMO of the Local Health Trust No. 8 of Cagliari, to conduct a clinical trial titled as specified above. The aforementioned Investigator will be assisted in carrying out the clinical trial by the registered

medical staff designed and supervised by the same Investigator. The designated medical staff have expressed their acceptance and will be, hereinafter, referred to as "co-investigators. The list of co-investigators will be kept updated by the Investigator. Pursuant to Ministerial Decree of 15/07/1997, the company appoints Dr. Barry Skikneas responsible of the clinical trial and medical contact who will be assuming the responsibilities set forth by Ministerial Decree of 15/07/1997) and subsequent amendments, domiciled by virtue of his/her position at the Company.

Article 3

The clinical trial shall be carried out in accordance with the ethical principles established by the Helsinki Declaration and subsequent amendments, in accordance with the Good Clinical Practice guidelines, with all applicable laws according to the Protocol provisions, reviewed and approved by the Responsible of the clinical study, as well as in compliance with the provisions of legislative Decree 211/2003 and to Legislative Decree 196/2003, to the extent this is applicable.

Art. 4

Prior to starting the clinical study, the Principal Investigator must obtain the required written informed consent from patients as well as the express consent to the processing of personal data.

Art. 5

The Company undertakes to supply the clinical trial medicinal products AZACITIDINE Oral free of charge, for the entire duration of the trial and in the required quantity. The quantities must be sufficient for the numbers of patients being treated.

Art. 6

By way of payment for the activities under this Agreement which provides for n.5 patients, the Company undertakes to pay the Local Health Authority by a bank transfer sent to **Banco Di Sardegna Servizio Tesoreria – Viale Bonaria - Cagliari Codice IBAN :IT29G0101504800000070188775**

in accordance with the amount as listed in Annex A.

Laboratory and diagnostic tests performed in the standard of care and used by Sponsor for clinical trial purposes must be equated to the extra-routinary ones and therefore these shall be borne to Sponsor as set forth article 7 Trust Regulation for the clinical trial management approved with Resolution No. 1773 dated 04/12/2014.the detailed list of the tests is reported in the annex to this Agreement. In the case of selected/randomized patients who withdraw from treatment earlier than specified by the Protocol, the Company will only pay the Trust an amount that is proportionate to the actual duration of treatment for each patient.

The amounts stated in Annex A shall be paid to the Trust, upon billing request from the Sponsor, sent also to the Principal Investigator for the verification of his/her competence, such request shall include the amount due and the clarification on whether this amount is to be referred to the end of the study or if this is an instalment of payment, in which case it must be stated the referring period. The billing request should also detail the method of calculating the amount payable to the Trust (ie number of patients per unit cost, number of tests divided by type and unit cost). At the billing request will follow the issuance of a notice of payment by the Trust and only after receipt of the transfer an invoice will be issued. The reason for payment should contain the protocol number of the payment notice issued by the Trust and the name of the Principal Investigator.

Art. 7

The Company states that an appropriate insurance policy (No ITCANP01345 Expiry date 30 June 2017) with ACE European Group Limited has been taken out, the policy covers the damage up to a maximum of one million Euro per person and five million Euro for Protocol.

"This limitation does not affect in any way the right of the damaged subject to obtain compensation from the party responsible for such damage" article 1 section 6 Decree 14 July 2009.

to cover civil liability claims for damages to people or properties resulting from their participation in the trial, including costs for medical treatment of patients taking part in the trial, even after it ended, in

the event of any complications caused by the trial itself. The Company releases the Trust and its employees from any liability related to the trial, except for damage attributable to wilful misconduct of the investigators or other employees, according to letter f) of Legislative Decree No. 211/2003, to DM 14 July 2009 and by all applicable laws; without prejudice to a more comprehensive insurance coverage guaranteed by the policies in effect. The Company undertakes to send a copy of the insurance policy renewal throughout the duration of the trial.

Art. 8

This agreement shall take effect from the date of signature and will end upon the completion of the research study scheduled for July 2018, subject to extension or early termination by mutual agreement.

However, either party may withdraw from this agreement prior to its expiration by giving appropriate notice in writing by registered letter with advice of receipt. In the event of early withdrawal, the Company shall pay the Trust for documented non-revocable expenses that have already been incurred during the conduct of the clinical trial and shall be entitled to receive, as the original owner, all complete and partial results achieved by the Trust, within 30 days from termination of the agreement.

No other claim may be made by the parties hereto as a result of an early termination of the agreement. The Company will be responsible for the payment of charges and taxes related to, and resulting from, this agreement, including stamp duty and filing fees, where required.

Art. 9

The Trust and the Investigator undertake to observe the confidentiality of all information received from the Company, or obtained during the trial, about the product or the results of the trial. The results must be always discussed by the clinical trial director (and/or Research group), together with the Representative of the Company prior to publication and in any event no publication shall be even considered until all patients at all the sites have completed the trial and the data has been processed.

The Trust, the Investigator, on its behalf, and the Company also undertake to maintain the confidentiality of personal information of which they may become aware for any reason during the trial, in accordance with the requirements of Decree 196/2003 governing the protection of personal information, as amended.

In accordance with Legislative Decree 196/2003 "*Regulations governing the protection of personal information*", as well as with the deliberation of the Governing Authority (Deliberation 52 of 24/7/08), the Trust and the Sponsor, each within its own area of responsibility, are independent Data Controllers for the handling of data related to the Clinical Trial hereunder.

The Sponsor/CRO agrees to:

a) Handle the data primary for research purposes;

b) fulfil the obligations set forth in the Code governing the protection of personal data;

c) Comply with any specific instructions received in reference to the handling of personal data;

d) Inform about the safety measures adopted and any subsequent amendment;

e) Inform immediately the Local Health Trust n.8 of Cagliari in the event of abnormal or emergency situations.

Art. 10

The Trial Director shall keep the Company informed about the progress of the research and shall notify the Company and the CRO of any adverse events or serious side effects which may occur during the trial and that are directly or indirectly attributable to the administration of the product to patients under observation.

Art. 11

In case of conflict between this Agreement and the Protocol, the Protocol shall prevail in matters concerning science and conduct of the study. For all other conflicts, priority goes to the terms of this Agreement. The competent authority for any dispute arising from the interpretation and execution of this agreement, which cannot be settled amicably, will be the Court of Cagliari.

Art. 12

Any significant amendment to this agreement must be made in writing. This agreement shall be signed, in acceptance, by the parties hereto and by the clinical trial Director. Filing and stamp duties shall be borne by the Company, if this agreement is to be used.

For the **Local Health Trust. n. 8**

The Special Commissioner

Dr. Savina Ortu

Date: _____

The **Principal Investigator** (in acceptance)

Prof. Emanuele Angelucci

Date: Feb 10, 2015

For the **Sponsor**

Isabelle Coudert

Director Clinical Monitoring EU

Date: 04 Feb 2015

ANNEX A

BUDGET AND PAYMENT TERMS & CONDITIONS

Celgene Protocol No. AZA-MDS-003
Investigator Name: Prof. Emanuele Angelucci
Institution Name: Ospedale Oncologico A. Businco
Per Completed Study Participant: € 8,737.00
Number of Estimated Enrolled: 5

Payments shall be made quarterly, based upon the terms below. The amounts below are payable by the Sponsor to Trust pursuant to Section 6 of this Agreement only, i.e. in consideration of the conduct of the Study by Trust/Investigator under this Agreement. All sums are in "Currency EURO" (€).

The following additional payments are permitted upon approval of submitted invoices:

Screen Failure: A Screen Failure shall be defined as a Study Participant who has signed an Informed Consent but could not be effectively included in the Study under the inclusion/exclusion criteria or for other reasons. A maximum of 2 Screen Failures shall be paid during the study at a rate of € 857.00 per Screen Failure Subject.

Unscheduled Visits: For additional visits or procedures that are unscheduled, payment shall be made on a case-by-case basis, upon prior written authorization from Sponsor / CRO. Invoices for authorized unscheduled visits must be provided for reimbursement.

Laboratory Costs: A fee for collecting and processing samples is included in the patient budget. The samples shall be analyzed in a central laboratory and no analytic costs shall therefore be incurred by the Trust.

DETAILED BUDGET - VISIT SCHEDULE & INVOICABLE ITEMS

Period	Visit		Visit Cost
	Screening & Randomization		€ 1,143.00
Treatment phase	Cycle 1	Day 1	€ 478.00
		Day 8	€ 156.00
		Day 15	€ 156.00
		Day 22	€ 156.00
	Cycle 2	Day 1	€ 478.00
		Day 8	€ 156.00
		Day 15	€ 156.00
		Day 22	€ 156.00
	Cycle 3	Day 1	€ 908.00
		Day 15	€ 156.00
	Cycle 4	Day 1	€ 435.00
		Day 15	€ 156.00
	Cycle 5	Day 1	€ 435.00
		Day 15	€ 156.00
	Cycle 6	Day 1	€ 925.00
		Day 15	€ 156.00
	Cycle 7	Day 1	€ 435.00
		Day 15	€ 156.00
	Cycle 8	Day 1	€ 435.00
		Day 15	€ 156.00
	Treatment Discontinuation		€ 753.00
Follow Up phase	Follow Up Month 1		€ 55.00
	Follow Up Month 2		€ 55.00
	Follow Up Month 3		€ 55.00
	Follow Up Month 4		€ 55.00
	Follow Up Month 5		€ 55.00
	Follow Up Month 6		€ 55.00
	Follow Up Month 7		€ 55.00
	Follow Up Month 8		€ 55.00
Total	Includes completion of Cycles 1-8, Treatment Discontinuation, & 8 Follow-up visits		€ 8,737.00

All subjects discontinued from treatment for any reason will be followed for survival, subsequent MDS therapies, progression to AML, and SPM. After the discontinuation visit has been performed, only follow-up visits could be performed on subject.

Biomarkers Optional procedures

Optional Procedure	Visit	Cost
Peripheral Blood Sample	Day 1 of Cycles 3, 6, and 12, and every 6 cycles thereafter (eg, Day 1 of Cycles 18, 24, etc.) and Day 15 of Cycles 3, 6, and 12	€30.00 per procedure
Bone Marrow Sample	Day 1 of Cycles 3, 6, and 12, and very 6 cycles thereafter (eg, Day 1 of Cycles 18, 24, etc.)	€30.00 per procedure

Additional cycles:

Period	Visit		Visit Cost
Treatment phase	Cycle 9-11	Day 1	€ 435.00
		Day 15	€ 156.00
	Cycle 12	Day 1	€ 470.00
		Day 15	€ 156.00
	Cycle13+		€ 445.00
Follow Up phase	Follow Up, Months 9+		€ 55.00

The sums shown include all payments due in connection with the conduct of the Study, including pharmacy payments, unless otherwise indicated. For the avoidance of doubt the sums shown include all payments due for any and all examinations, including but not limited to those examinations which may incur an extra cost on the Trust. In such case the Company/CRO shall communicate it in the invoice request.

Payee (Institution):	Azienda U.S.L. N. 8 di Cagliari
Address:	Selargius (Su Planu), Via Piero della Francesca, 1
Payee Contact Name:	XXXXX
Telephone Number:	XXXXX

VAT Registration Number (if applicable):	02261430926

DETAILS FOR PAYMENT BY BANK TRANSFER

Account holder:	Azienda U.S.L. N. 8 di Cagliari
Account No.:	XXXXX
Bank:	Banco Di Sardegna Servizio Tesoreria – Viale Bonaria - Cagliari
Sort Code:	XXXXX
IBAN:	IT29G0101504800000070188775
BIC (SWIFT) Code:	BPMOIT22XXX

Invoice Information

Original invoices pertaining to this Study shall be headed to: Celgene and submitted for payment to the following address:

Celgene International Sarl
c/o PPD Central Investigator Payments
929 North Front Street
Wilmington NC 28401
USA

All invoices must include the following information and corresponding receipts:

Protocol Number: AZA-MDS.003
Investigator Name: Prof. Emanuele Angelucci
Institution Name: Azienda U.S.L. N. 8 di Cagliari
Address: Selargius (Su Planu), Via Piero della Francesca, 1
Payee Contact Information: XXXXX
Name & Telephone Number: XXXXX
Total Number of Participants: 5
Cost per Study Participant (excluding tax): € 8.737,00
Institution VAT Number (if applicable): 02261430926

GENERAL PAYMENT TERMS:

i) Payments will be made every three months upon receipt of a valid VAT invoice.

ii) All costs mentioned here are net costs, excluding VAT.

iii) The remuneration is to be declared for tax assessment by the payee. The relevant income tax regulations should be taken into account.

ANNEX B
EQUIPMENT PROVIDED TO THE INSTITUTION

Sponsor will provide, under free loan, site with the following:

- n.1 TAB for questionnaire filling out on life quality in electronic version, Model CL910 – SitePro Tablet supplied by Invivo Data, commercial value Euro 832.00;
- n. 1 Thermometer, Model RT801, supplied by Re5al BV, (commercial value: € 15.00)

TIMELINES

(Section 2.1.1)

Planned First Subject Screened: Nov 2012

Planned First Subject Randomized: Dec 2012

Planned Last Subject Randomized: Dec 2016

Planned Last Subject Last Visit: Jul 2018

Planned Last CFR in House) : TBC

ALLEGATO ALLA DELIBERAZIONE

N. 251 DEL 25 FEB. 2015

IL DIRETTORE AMMINISTRATIVO
Dott.ssa Antonella Carreras

IL DIRETTORE SANITARIO
Dott. Pier Paolo Pani

IL COMMISSARIO STRAORDINARIO
Dott.ssa Savina Ortu

Il presente allegato è composto da n° 14 fogli di n° 14 pagine.