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| **STUDY INFORMATION** | |
| Promoter | Università degli studi di Milano-Bicocca |
| Protocol code |  |
| Study name |  |
| pCRF version | v. X.X, XX/XX/XXXX |
| Protocol version | v. X.X, XX/XX/XXXX |

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| **STUDY TITLE** |
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| **INCLUSION AND EXCLUSION CRITERIA** |
| **Inclusion criteria** |
| 1. Subject must be at least 18 years of age at study beginning |
| 1. Male subject must be at least 18 years old at study beginning |
| 1. Female subject must be at least 18 years old at study beginning |
| 1. Female subjects of child-bearing potential must agree to use a medically accepted method of contraception. |
| 1. Female subjects of child-bearing potential must have a negative serum beta-hCG pregnancy test at Screening, and a negative urine beta-HCG pregnancy test on Day 1 prior to dosing. |
| 1. Subject must be able to adhere to dose and visit schedules. |
| 1. Informed consent freely provided before study beginning. |
| **Exclusion criteria** |
| 1. Female subjects of childbearing potential who are breastfeeding, pregnant, or planning to become pregnant. |
| 1. Subjects with any clinically significant condition or situation other than the condition being studied that, in the opinion of investigator, would interfere with the study evaluations or optimal participation. |
| 1. Subject is taking or plans to take any of the prohibited medications listed in the protocol. |
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| **Form name** | **General instructions** |
| **General** | |
| A CRF must be completed for each study participant who is enrolled.  For reasons of confidentiality, the name and initials of the study participant must not appear on the CRF.  If the answer to a question is unknown, write “NK” (Not Known).  If a requested test has not been done, write “ND” (Not Done).  If a question is not applicable, write “NA” (Not Applicable). | |
| **Completion instructions** | |
| Please print all entries in BLOCK CAPITAL LETTERS using a black or blue ballpoint pen. All text and explanatory comments should be brief.  Answer every question explicitly; do not use ditto marks. Do not leave any question unanswered. | |
| **Correction of errors** | |
| If an error is recorded, crossing out the incorrect entry with a single horizontal line, placing the correct information next to the error, and providing an initial and date next to the correction. Do not backdate. Do not use any type of correction fluid or erase any entries on the forms. | |
| **Fields kind and completion instructions** | |
| **Free text field**: \_\_\_\_\_\_\_\_ write in English, please.  **Numeric field:** |\_\_\_|\_\_\_|\_\_\_| . |\_\_\_| respect decimal position if it is applicable. If the boxes number exceeds digits number leave it blank, or fill with a 0 on the first box on the left, as you prefer.)  i.e. |\_\_\_|\_8\_|\_3\_| . |\_0\_| Kg O |\_0\_|\_8\_|\_3\_| . |\_0\_| Kg  **Radio button:**  (only one choice is allowed, you can tick V or you can check X the radio button.)  i.e. Yes X No or Yes V No  **Check box:**  (multiple choices are allowed, you can tick V or you can check X the check box.)  i.e. X Bones Lungs Skin or V Bones Lungs Skin  **Date: |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|**  All date entries must appear in the format DD-MMM-YYYY e.g. 05-May-2009. The month  abbreviations are as follows:  January= JAN April= APR July= JUL October= OCT  February= FEB May= MAY August= AUG November= NOV  March= MAR June= JUN September= SEP December= DEC  i.e. |0|2|/|A|U|G|/|2|0|1|8|  D D M M M Y Y Y Y | |

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| **Form name** | **FLOW CHART - PATIENT REGISTRATION – VISIT** |

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| **Form name** | **FLOW CHART** | | | | | |
| pCRF sections | Visit No. | V1 | V2 | V3 | V4 | V5 |
| Visit ID | Baseline/ screening | ID 2 | ID 3 | ID 4 | Follow-up |
| Time unit | X | X | X | X | X |
| Patient registration | | X |  |  |  |  |
| Visit | | X | X | X | X | X |
| Demographic | | X |  |  |  |  |
| Vital signs | | X | X | X | X | X |
| Patient habits | | X |  |  |  |  |
| Medical History | | X |  |  |  |  |
| Cardiac ultrasound | | X |  |  |  |  |
| Lab tests | | X | X | X | X | X |
| Inclusion/ exclusion criteria | | X |  |  |  |  |
| Randomization | | X |  |  |  |  |
| Drug administration | | X | X | X | X | X |
| Drug accountability | | X | X | X | X | X |
| General physical examination | | X | X | X | X | X |
| Activities of Daily Living Index | | X |  |  |  |  |
| Short Physical Performance Battery | | X |  |  |  |  |
| Mini Mental State Evaluation | | X |  |  |  |  |
| Signature | | X | X | X | X | X |
| Adverse Event | | XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | | | | |
| Concomitant drugs | | XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | | | | |
| Study discontinuation | | XXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXXX | | | | |

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| **Section name: Patient registration** | |
| ID centre | **|\_\_|\_\_|\_\_|\_\_|** |
| ID patient | **|\_\_|\_\_|\_\_|\_\_|** |
| Did the patient signed the informed consent ? | ⃝ Yes ⃝ No |
| Informed consent date | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y |
| Attention: Inclusion criteria n. x: … | |

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| **Section name: Visit** | |
| Visit date | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y |

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| **Form name** | **DEMOGRAPHIC - VITAL SIGNS** |

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| **Section name: Demographic** | |
| BIRTHDATE | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y |
| Attention: Inclusione criteria n. x: AGE ≥ xx years. | |
| SEX | ⃝ Female ⃝ Male ⃝ Transgender  ⃝ Refuse to reply ⃝ Indeterminable ⃝ Not known |
| ETNICITY | ⃝ Asiatic ⃝ Black ⃝ White  ⃝ Other, specify:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  ⃝ Not known |
| STUDY LEVEL | ⃝ Early childhood education  ⃝ Primary  ⃝ Lower secondary  ⃝ Upper secondary  ⃝ Post-secondary non-tertiary  ⃝ Short-cycle tertiary  ⃝ Bachelor or equivalent  ⃝ Master or equivalent  ⃝ Doctoral or equivalent  ⃝ Not known |

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| **Section name: Vital Signs** | |
| **Vital factors** | **Values** |
| Systolic pressure | |\_\_|\_\_|\_\_| mmHg |
| Diastolic pressure | |\_\_|\_\_|\_\_| mmHg |
| Heart rate | |\_\_|\_\_|\_\_| bpm |
| Respiratory rate | |\_\_|\_\_|\_\_| breaths/ minutes |
| Height | |\_\_|\_\_|\_\_| cm |
| Weight | |\_\_|\_\_|\_\_| Kg |

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| **Form name** | **PATIENT HABITS - MEDICAL HISTORY** |

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| **Section name: Patient Habits** | |
| SMOKE | ⃝ Smoker  ⃝ Ex-smoker (less than one year)  ⃝ Ex- smoker (more than one year)  ⃝ Never smoked ⃝ Not known |
| ALCOHL | ⃝ Soft drinker (one/ two glasses/ day)  ⃝ Moderate drinker (three glasses/ day)  ⃝ Hard drinker (four or more glasses/ day)  ⃝ Teetotaller ⃝ Not known |

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| **Section name: Medical history – Part 2** | |
| Diabetes mellitus | ⃝ None ⃝ Uncomplicated ⃝ End-organ damage |
| Liver disease | ⃝ No ⃝ Mild ⃝ Moderate to severe |
| Malignancy | ⃝ None  ⃝ Any leukemia, lymphoma, or localized solid  tumor  ⃝ Metastatic solid tumor |
| AIDS | ⃝ No ⃝ Yes |
| Moderate to severe Chronic Kidney Disease | ⃝ No ⃝ Yes |
| Congestive Heart Failure | ⃝ No ⃝ Yes |
| Myocardial infarction | ⃝ No ⃝ Yes |
| Chronic Obstructive Pulmonary Disease | ⃝ No ⃝ Yes |
| Peripheral vascular disease | ⃝ No ⃝ Yes |
| Cerebrovascluar accident or TIA | ⃝ No ⃝ Yes |
| Dementia | ⃝ No ⃝ Yes |
| Hemiplegia | ⃝ No ⃝ Yes |
| Connective tissue disease | ⃝ No ⃝ Yes |
| Peptic ulcer disease | ⃝ No ⃝ Yes |

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| **Form name** | **CARDIAC ULTRASOUND** |

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| **Section name: Cardiac ultrasound** | |
| Does the subject have a cardiac ultrasound? | ⃝ Yes ⃝ No |
| If No, schedule the cardiac ultrasound and fill the section when it will be available | |
| What was the date of the last cardiac ultrasound? | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y |
| Ventricular Mass Index (MCI) | |\_\_|\_\_|\_\_| g/m2 ⃝ Not known |
| Left ventricular hypertrophy | ⃝ Yes ⃝ No |
| Attention.  Left ventricular hypertrophy is defined as:  - male MCI > 115 g/m2  - female MCI > 95 g/m2  - in the medical report | |
| Ejection Fraction (EF) | |\_\_|\_\_|\_\_| % ⃝ Not known |
| Left ventricular dysfunction | ⃝ Yes ⃝ No |
| Attention.  Left ventricular dysfunction is defined as:  - EF < 50%  - in the medical report | |
| Maximum left atrial diameter | |\_\_|\_\_|\_\_| mm ⃝ Not known |
| Left atrial diameter | |\_\_|\_\_|\_\_| mL/m2 ⃝ Not known |
| Atriomegaly | ⃝ Yes ⃝ No |
| Attention.  Atriomegaly is defined as:  - Maximum left atrial diameter sx >40 mm  - Left atrial diameter > 34 mL/m2  - in the medical report | |

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| **Form name** | **LAB TESTS** |

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| **Section name: Lab tests** | | | | | | |
| Does the subject have lab tests? | | | ⃝ Yes ⃝ No | | | |
| If No, schedule the test and fill the section when they will be available | | | | | | |
| When did the subject do the lab tests? | | | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y | | | |
| **Test** | **Value** | **Unit** | | **Range** | **Out of range?** | **Clinically relevant?** |
| Red blood cells | |\_\_|\_\_|.|\_\_| | 109/L | | |4|.|5|-|5|.|9| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| White blood cells | |\_\_|\_\_|.|\_\_| | 109/L | | |4|.|0|-|1|1|.|0| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Neutrophils | |\_\_|\_\_|.|\_\_| | 109/L | | |2|.|5|-|7|.|5| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Lymphocytes | |\_\_|.|\_\_| | 109/L | | |1|.|5|-|3|.|5| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Monocytes | |\_\_|.|\_\_| | 109/L | | |0|.|2|-|0|.|8| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Eosinophils | |\_\_|.|\_\_|\_\_| | 109/L | | |0|.|0|4|-|0|.|4| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Basophils | |\_\_|.|\_\_|\_\_| | 109/L | | |0|.|0|1|-|0|.|1| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Platelets | |\_|\_|\_|\_|\_|\_| | Cellule/µL | | |0|.|0|1|-|0|.|1| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Haemoglobin | |\_\_|\_\_|.|\_\_| | g/dL | | |1|4|.|0|-|1|7|.|5| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Albumin | |\_\_|.|\_\_| | g/dL | | |3|.|5|-|5|.|0| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Vitamin D | |\_\_|\_\_|\_\_| | ng/mL | | |3|0|-|1|0|0| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Urea | |\_\_|.|\_\_| | mmol/L | | |2|.|5|-|7|.|1| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Creatinin | |\_\_|\_\_|\_\_|.|\_\_| | mmol/L | | |7|4|.|3|-|1|0|7| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Sodium | |\_\_|\_\_|\_\_| | mEq/L | | |1|3|5|-|1|4|5| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Potassium | |\_\_|.|\_\_| | mEq/L | | |3|.|6|-|5|.|2| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| PCR | |\_\_|\_\_|\_\_| | mg/L | | <|8| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| ALT | |\_\_|\_\_| | U/L | | |7|-|5|5| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| AST | |\_\_|\_\_| | U/L | | |8|-|4|8| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| ALP | |\_\_|\_\_|\_\_| | U/L | | |4|5|-|1|1|5| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |
| Glucose | |\_\_|.|\_\_| | mmol/L | | >|7|.|8| | ⃝ Yes ⃝ No | ⃝ Yes ⃝ No |

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| **Form name** | **INCLUSION/ EXCLUSION CRITERIA** |

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| **Section name: Inclusion/ Exclusion criteria** | | |
| What was the date of inclusion/exclusion criteria evaluation? | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y | |
| **SubSection name: Inclusion criteria** | | |
| 1. Subject must be at least 18 years of age at study beginning | | ⃝ Yes ⃝ No |
| 1. Male subject must be at least 18 years old at study beginning | | ⃝ Yes ⃝ No |
| 1. Female subject must be at least 18 years old at study beginning | | ⃝ Yes ⃝ No |
| 1. Female subjects of child-bearing potential must agree to use a medically accepted method of contraception. | | ⃝ Yes ⃝ No |
| 1. Female subjects of child-bearing potential must have a negative serum beta-hCG pregnancy test at Screening, and a negative urine beta-HCG pregnancy test on Day 1 prior to dosing. | | ⃝ Yes ⃝ No |
| 1. Subject must be able to adhere to dose and visit schedules. | | ⃝ Yes ⃝ No |
| 1. Informed consent freely provided before study beginning. | | ⃝ Yes ⃝ No |
| **SubSection name: Exclusion criteria** | | |
| 1. Female subjects of childbearing potential who are breastfeeding, pregnant, or planning to become pregnant. | | ⃝ Yes ⃝ No |
| 1. Subjects with any clinically significant condition or situation other than the condition being studied that, in the opinion of investigator, would interfere with the study evaluations or optimal participation. | | ⃝ Yes ⃝ No |
| 1. Subject is taking or plans to take any of the prohibited medications listed in the protocol. | | ⃝ Yes ⃝ No |
|  | | ⃝ Yes ⃝ No |
|  | | ⃝ Yes ⃝ No |

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| **Form name** | **RANDOMIZATION - DRUG ADMINISTRATION – DRUG ACCOUNTABILITY** |

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| **Section name: Randomization** | |
| Eligible for randomization? | ⃝ Yes ⃝ No |
| If “Eligible for randomization?”= “Yes” will appear “Date of randomization” and “Randomization number” | |
| Date of randomization | Calendario giornaliero |
| Randomization number | |\_\_|\_\_|\_\_| |

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| **Section name: Drug administration** | |
| Does the subjected received the treatment administration? | ⃝ Yes ⃝ No |
| If Yes fill the rest, otherwise skip to the next section | |
| What was the date of the treatment administration? | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y |
| Notes | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |

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| **Section name: Drug accountability** | | | | | | |
| Does the subjected received the treatment box? | | | | ⃝ Yes ⃝ No | | |
| If Yes fill the rest, otherwise skip to the next section | | | | | | |
| What the date of the treatment box dispensation? | | | | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y | | |
| ID | Label number | Batch number | Treatment | | Tablet numbers | Treatment compliance? |
| 1 |  |  | |\_\_| | | |\_\_|\_\_| | ⃝ Si ⃝ No ⃝ NA |
| 2 |  |  | |\_\_| | | |\_\_|\_\_| | ⃝ Si ⃝ No ⃝ NA |
| Complition instructions:  A= treatment a; B= treatment b | | | | | | |
| Who did dispensed the treatment? | | | | Please, write in block letters | | |
| Attention:  The person who dispensed the treatment must be present in the delegation log | | | | | | |

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| **Form name** | **GENERAL PHYSICAL EXAMINATION** |

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| **Section name: General physical examination** | | | |
| Has been physical examination performed? | | ⃝ Yes ⃝ No | |
| If Yes fill the rest, otherwise skip to the next section | | | |
| When was the date of the general physical examination? | | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y | |
| Who did the general physical examination? | | Please, write in block letters | |
| **Sistema** | **System status** | | **If Abnormal, specify** |
| General | ⃝ Normal ⃝ Abnormal | | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Head and neck  (mouth, throat, eyes, ears) | ⃝ Normal ⃝ Abnormal | | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Thorax  (lungs, heart, stomach) | ⃝ Normal ⃝ Abnormal | | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Abdomen  (liver, spleen, kidneys, gut, urogenital) | ⃝ Normal ⃝ Abnormal | | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Extremities | ⃝ Normal ⃝ Abnormal | | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |

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| **Form name** | **SIGNATURE** |

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| **Section name: Signature** | |
| Signing this form I declare that I inserted and reviewed the CRF data in the best accurate and complete form and that the information are the same with respect to medical report. | |
| When was the date of the signature? | |\_\_|\_\_|/|\_\_|\_\_|\_\_|/|\_\_|\_\_|\_\_|\_\_|  D D / M M M / Y Y Y Y |
| Signature | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| What is the name of the physician present at the moment of the enrolment? | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |