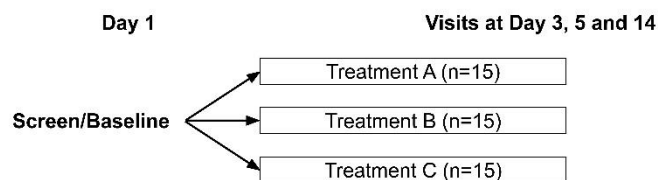


## Supplementary data

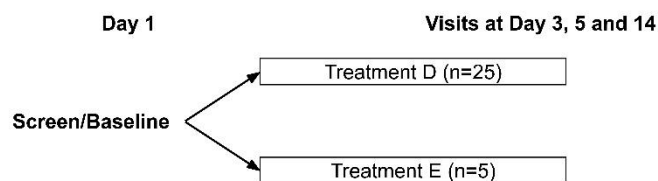
**Figure S1:** Study design.

### Cohort 1 study design



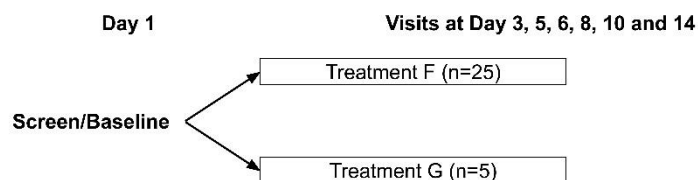
Treatment A = single 75 mg dose of acumapimod on Day 1 + prednisone placebo x 10 days  
Treatment B = single dose acumapimod placebo on Day 1 + prednisone placebo x 10 days  
Treatment C = single dose acumapimod placebo on Day 1 + 40 mg oral prednisone x 10 days

### Cohort 2 study design



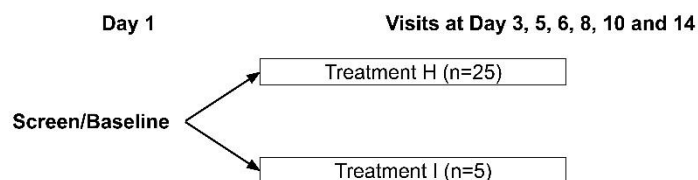
Treatment D = single 20 mg dose of acumapimod on Day 1  
Treatment E = single dose acumapimod placebo on Day 1

### Cohort 3 study design



Treatment F = single 20 mg dose of acumapimod on Day 1 and Day 6  
Treatment G = single dose acumapimod placebo on Day 1 and Day 6

### Cohort 4 study design



Treatment H = single 75 mg dose of acumapimod on Day 1 and Day 6  
Treatment I = single dose acumapimod placebo on Day 1 and Day 6

**Table S1.** Study investigators (by country in alphabetical order)

| Country  | Investigators                                                                                                                                                                                                                                                               | Institution                                                                                                                                                                                                                                                                                                                                            |
|----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bulgaria | Dr Hristo Metev (primary investigator)<br>Dr Dimitar Getov<br>Dr Robert Shikov<br>Dr Nikolay Evgeniev<br>Dr Elena Docheva<br>Dr Antonia Gramatikova                                                                                                                         | Specialised Hospital for Active Treatment of Pneumophysiatrie Diseases, Rousse EOOD, 7000, Bulgaria                                                                                                                                                                                                                                                    |
| Bulgaria | Dr Veselin Davchev (primary investigator)<br>Dr Mariya Dimitrova-Georgieva (primary investigator)<br>Dr Krasimira Penevska-Kasparyan<br>Dr Boyka Stanimirova Georgieva-Davazkova<br>Veneta Velinova Valeva-Kalcheva<br>Petaz Alexandzov Petozv<br>Albena Kancheva Kichukova | Specialised Hospital for Pneumophysiatrie Diseases and Active Treatment, Dimiter Kudoglu, Pneumology Department, 108 Tsarigradsko shose blvd, Plovdiv 4000, Bulgaria<br><br>Site moved to (May 2012)<br>Multiprofile Hospital for Active Treatment-Medical Center, Department of Internal Diseases, 144 A-A, Vasil Levski str., 4003 Plovdiv, Bulgaria |
| Bulgaria | Darinka Dimova (primary investigator)<br>Petar Atanassov                                                                                                                                                                                                                    | Specialised Hospital for Pneumophysiatrie Diseases and Active Treatment. Dimiter Kudoglu, Pneumology Department, 108 Tsarigradsko shose blvd, Plovdiv 4000, Bulgaria                                                                                                                                                                                   |

|         |                                                                                                                                                                                                                                                                      |                                                                     |
|---------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| Romania | Dr Irina Strambu (primary investigator)<br>Dr Diana Ionita<br>Dr Ileana Stoicescu<br>Dr Ana-Maria Sasu<br>Dr Emilia Tabacu<br>Dr Mihaela-Carmen Mitrea<br>Dr Daniela Dospinoiu<br>Dr Felicia Cojocarui<br>Dr Camelia Nita<br>Dr Madalina Burecu<br>Dr Alina Croitoru | Institute of Pneumology, "Marius Nasta", Bucharest, 050159, Romania |
| Russia  | Zhanna Kobalava (principal investigator)<br>Elena Shavarova<br>Ph.D Tatiana Dmitrova<br>Tina Lobzhanidze<br>Elena Troitskaya<br>Ruslan Kobzev<br>Anna Klimenko<br>Svetlana Avdoshina                                                                                 | City Clinical Hospital #64, Moscow, 117292, Russia                  |
| Russia  | Valentin Moiseev (principal investigator)<br>Dr Lale Babaeva<br>Elena Styrt<br>Ivan Goncharova<br>Christina Isikova                                                                                                                                                  | Clinical Hospital #3, (Medsanchast #47), Moscow, 117192, Russia     |
| Russia  | Bagdadi Alikhanov (principal investigator)<br>Alla Vavilina<br>Lala Karapetyan<br>Andrey Ivanov<br>Leonty Kitsenko                                                                                                                                                   | Central Military Clinical, Hospital No. 3, Moscow, 107014, Russia   |

|        |                                                                                                                |                                                                                                              |
|--------|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|
|        | Mikhail Sandin                                                                                                 |                                                                                                              |
| Russia | Alexander Emelyanov (primary investigator)<br>MD Antonina Znakhurenko<br>Evgenia Leshenkova<br>Galina Sergeeva | Saint-Petersburg Medical, Academy of Advanced Studies under MoH Metropolitan, St. Petersburg, 189216, Russia |

**Table S2: Patient hospitalization rates (PD analysis set)**

| Parameter                                               |                            | Treatment group                                |                                                |                                 |                                                |                                                |                     |
|---------------------------------------------------------|----------------------------|------------------------------------------------|------------------------------------------------|---------------------------------|------------------------------------------------|------------------------------------------------|---------------------|
|                                                         |                            | 20 mg<br>single-dose<br>acumapimod<br>(n = 25) | 20 mg<br>repeat-dose<br>acumapimod<br>(n = 27) | 40 mg<br>prednisone<br>(n = 30) | 75 mg<br>single-dose<br>acumapimod<br>(n = 31) | 75 mg<br>repeat-dose<br>acumapimod<br>(n = 25) | Placebo<br>(n = 45) |
| <b>Length of initial<br/>hospitalization<br/>(days)</b> | n (%)                      | 7 (28.0)                                       | 11 (40.7)                                      | 14 (46.7)                       | 14 (45.2)                                      | 12 (48.0)                                      | 18 (40.0)           |
|                                                         | Mean                       | 11.9                                           | 12.8                                           | 13.4                            | 11.1                                           | 11.6                                           | 12.4                |
|                                                         | SD                         | 2.34                                           | 3.19                                           | 6.15                            | 2.71                                           | 2.94                                           | 5.20                |
|                                                         | Min                        | 10                                             | 10                                             | 10                              | 7                                              | 10                                             | 10                  |
|                                                         | Median                     | 10.0                                           | 14.0                                           | 10.0                            | 10.0                                           | 10.0                                           | 10.0                |
|                                                         | Max                        | 15                                             | 20                                             | 33                              | 17                                             | 18                                             | 30                  |
| <b>One-sided 10%<br/>Wilcoxon test, n<br/>(%)</b>       | p-value<br>versus<br>group | 0.261                                          | 0.091                                          | 0.161                           |                                                | 0.413                                          | 0.347               |
|                                                         |                            | 0.344                                          | 0.144                                          | 0.223                           |                                                | 0.446                                          |                     |
|                                                         |                            | 0.370                                          | 0.453                                          |                                 |                                                | 0.243                                          |                     |
|                                                         |                            |                                                | 0.328                                          |                                 |                                                | 0.380                                          |                     |
|                                                         |                            |                                                |                                                |                                 |                                                | 0.172                                          |                     |

n = all observations non-missing

PD, pharmacodynamics

**Table S3. Selected biomarkers**

**IL-6 (pg/mL) (Part 1 of study only, PD analysis set)**

| Visit  |           | Treatment Group                                |                     |                                   |                    |
|--------|-----------|------------------------------------------------|---------------------|-----------------------------------|--------------------|
|        |           | 75 mg<br>single-dose<br>acumapimod<br>(n = 31) | Placebo<br>(n = 45) | 40 mg<br>prednisolone<br>(n = 30) | Total<br>(n = 183) |
| Day 1  | n         | 31                                             | 30                  | 30                                | 91                 |
|        | Mean (SD) | 4.62 (3.84)                                    | 17.47 (59.57)       | 5.63 (4.42)                       | 9.19 (34.48)       |
| Day 5  | n         | 30                                             | 30                  | 30                                | 90                 |
|        | Mean (SD) | 3.02 (2.83)                                    | 3.88 (3.09)         | 2.60 (1.62)                       | 3.16 (2.62)        |
| Day 14 | n         | 27                                             | 30                  | 29                                | 86                 |
|        | Mean (SD) | 6.43 (6.43)                                    | 4.09 (3.35)         | 9.75 (5.85)                       | 6.73 (5.78)        |
| Day 30 | n         | 29                                             | 28                  | 27                                | 84                 |
|        | Mean (SD) | 5.05 (4.14)                                    | 3.39 (2.00)         | 5.53 (4.27)                       | 4.65 (3.69)        |
| Day 90 | n         | 19                                             | 19                  | 18                                | 56                 |
|        | Mean (SD) | 4.54 (2.62)                                    | 3.44 (2.91)         | 4.21 (2.11)                       | 4.06 (2.57)        |

n = all observations non-missing

PD, pharmacodynamics

# High sensitivity C-reactive protein (hsCRP, mg/mL) (PD analysis set)

| Visit  |           | Group                                          |                     |                                   |
|--------|-----------|------------------------------------------------|---------------------|-----------------------------------|
|        |           | 75 mg<br>single-dose<br>acumapimod<br>(n = 31) | Placebo<br>(n = 45) | 40 mg<br>prednisolone<br>(n = 30) |
| Day 1  | n         | 31                                             | 45                  | 30                                |
|        | Mean (SD) | 0.0079 (0.0091)                                | 0.0151 (0.0331)     | 0.0112 (0.0141)                   |
| Day 5  | n         | 31                                             | 45                  | 30                                |
|        | Mean (SD) | 0.0031 (0.0054)                                | 0.0109 (0.0190)     | 0.0029 (0.0031)                   |
| Day 14 | n         | 31                                             | 45                  | 30                                |
|        | Mean (SD) | 0.0159 (0.0248)                                | 0.0093 (0.0161)     | 0.0257 (0.0224)                   |
| Day 30 | n         | 31                                             | 45                  | 28                                |
|        | Mean (SD) | 0.0099 (0.0141)                                | 0.0065 (0.0081)     | 0.0142 (0.0332)                   |
| Day 90 | n         | 31                                             | 44                  | 26                                |
|        | Mean (SD) | 0.0081 (0.0097)                                | 0.0050 (0.0065)     | 0.0143 (0.0331)                   |

n = all observations non-missing

PD, pharmacodynamics

# High sensitivity C-reactive protein (hsCRP, mg/mL) (PD analysis set)

| Visit  |           | 20 mg<br>single-dose<br>acumapimod<br>(n = 25) | 20 mg<br>repeat-dose<br>acumapimod<br>(n = 27) | 75 mg<br>repeat-dose<br>acumapimod<br>(n = 25) | Total<br>(n = 183) |
|--------|-----------|------------------------------------------------|------------------------------------------------|------------------------------------------------|--------------------|
| Day 1  | n         | 25                                             | 27                                             | 25                                             | 183                |
|        | Mean (SD) | 0.0122 (0.0216)                                | 0.0071 (0.0067)                                | 0.0198 (0.0295)                                | 0.0123 (0.0226)    |
| Day 5  | n         | 25                                             | 26                                             | 25                                             | 182                |
|        | Mean (SD) | 0.0060 (0.0106)                                | 0.0029 (0.0036)                                | 0.0055 (0.0091)                                | 0.0057 (0.0115)    |
| Day 14 | n         | 25                                             | 26                                             | 25                                             | 182                |
|        | Mean (SD) | 0.0084 (0.0090)                                | 0.0147 (0.0236)                                | 0.0266 (0.0686)                                | 0.0161 (0.0317)    |
| Day 30 | n         | 25                                             | 25                                             | 24                                             | 178                |
|        | Mean (SD) | 0.0063 (0.0085)                                | 0.0081 (0.0073)                                | 0.0179 (0.0313)                                | 0.0101 (0.0195)    |
| Day 90 | n         | 24                                             | 25                                             | 22                                             | 172                |
|        | Mean (SD) | 0.0060 (0.0094)                                | 0.0075 (0.0092)                                | 0.0166 (0.0467)                                | 0.0089 (0.0223)    |

n = all observations non-missing

PD, pharmacodynamics



**Pro-calcitonin (ng/mL) (PD analysis set)**

|        |           | Group                                          |                     |                                   |
|--------|-----------|------------------------------------------------|---------------------|-----------------------------------|
|        |           | 75 mg<br>single-dose<br>acumapimod<br>(n = 31) | Placebo<br>(n = 45) | 40 mg<br>prednisolone<br>(n = 30) |
| Visit  | n         | 22                                             | 36                  | 24                                |
|        | Mean (SD) | 0.05 (0.03)                                    | 0.04 (0.02)         | 0.04 (0.02)                       |
| Day 1  | n         | 15                                             | 37                  | 22                                |
|        | Mean (SD) | 0.04 (0.02)                                    | 0.03 (0.01)         | 0.03 (0.01)                       |
| Day 5  | n         | 22                                             | 33                  | 27                                |
|        | Mean (SD) | 0.06 (0.09)                                    | 0.03 (0.01)         | 0.04 (0.02)                       |
| Day 14 | n         | 19                                             | 30                  | 18                                |
|        | Mean (SD) | 0.06 (0.06)                                    | 0.03 (0.01)         | 0.04 (0.01)                       |
| Day 30 | n         |                                                | 15                  |                                   |
|        | Mean (SD) |                                                | 0.03 (0.02)         |                                   |
| Day 90 | n         |                                                |                     |                                   |
|        | Mean (SD) |                                                |                     |                                   |

n = all observations non-missing

PD, pharmacodynamics

**Pro-calcitonin (ng/mL) (PD analysis set)**

| Visit  |           | 20 mg<br>single-dose<br>acumapimod<br>(n = 25) | 20 mg<br>repeat-dose<br>acumapimod<br>(n = 27) | 75 mg<br>repeat-dose<br>acumapimod<br>(n = 25) | Total<br>(n = 183) |
|--------|-----------|------------------------------------------------|------------------------------------------------|------------------------------------------------|--------------------|
| Day 1  | n         | 25                                             | 26                                             | 25                                             | 158                |
|        | Mean (SD) | 0.04 (0.02)                                    | 0.04 (0.02)                                    | 0.05 (0.03)                                    | 0.04 (0.02)        |
| Day 5  | n         | 25                                             | 26                                             | 25                                             | 150                |
|        | Mean (SD) | 0.03 (0.02)                                    | 0.03 (0.02)                                    | 0.02 (0.02)                                    | 0.03 (0.02)        |
| Day 14 | n         | 25                                             | 26                                             | 25                                             | 158                |
|        | Mean (SD) | 0.04 (0.02)                                    | 0.05 (0.07)                                    | 0.05 (0.06)                                    | 0.05 (0.05)        |
| Day 30 | n         | 25                                             | 25                                             | 24                                             | 141                |
|        | Mean (SD) | 0.03 (0.02)                                    | 0.04 (0.03)                                    | 0.05 (0.04)                                    | 0.04 (0.03)        |
| Day 90 | n         | 24                                             | 25                                             | 23                                             | 87                 |
|        | Mean (SD) | 0.03 (0.02)                                    | 0.04 (0.03)                                    | 0.04 (0.03)                                    | 0.04 (0.03)        |

n = all observations non-missing

PD, pharmacodynamics

# **Fibrinogen (g/L) (Safety analysis set)**

|        |           | Group                                          |                     |                                   |
|--------|-----------|------------------------------------------------|---------------------|-----------------------------------|
|        |           | 75 mg<br>single-dose<br>acumapimod<br>(n = 31) | Placebo<br>(n = 45) | 40 mg<br>prednisolone<br>(n = 30) |
| Day 1  | n         | 30                                             | 43                  | 30                                |
|        | Mean (SD) | 4.688 (2.0327)                                 | 4.482 (1.3283)      | 4.271 (0.9797)                    |
| Day 5  | n         | 31                                             | 44                  | 30                                |
|        | Mean (SD) | 3.662 (1.5444)                                 | 4.308 (1.4933)      | 3.512 (0.7731)                    |
| Day 14 | n         | 31                                             | 35                  | 29                                |
|        | Mean (SD) | 4.076 (1.3353)                                 | 4.214 (1.1024)      | 4.532 (1.0591)                    |
| Day 30 | n         | 23                                             | 18                  | 19                                |
|        | Mean (SD) | 4.277 (1.5143)                                 | 4.206 (1.1373)      | 4.782 (1.0262)                    |
| Day 90 | n         | 15                                             | 13                  | 16                                |
|        | Mean (SD) | 4.271 (1.0955)                                 | 4.214 (1.1094)      | 4.291 (1.1135)                    |

The repeated measurements are not taken into account for the calculation of the statistics

# **Fibrinogen (g/L) (Safety analysis set)**

| Visit  |           | 20 mg<br>single-dose<br>acumapimod<br>(n = 25) | 20 mg<br>repeat-dose<br>acumapimod<br>(n = 27) | 75 mg<br>repeat-dose<br>acumapimod<br>(n = 25) |
|--------|-----------|------------------------------------------------|------------------------------------------------|------------------------------------------------|
| Day 1  | n         | 25                                             | 26                                             | 25                                             |
|        | Mean (SD) | 3.909 (1.4500)                                 | 3.998 (1.2012)                                 | 4.458 (1.6098)                                 |
| Day 5  | n         | 24                                             | 23                                             | 22                                             |
|        | Mean (SD) | 3.500 (1.0492)                                 | 3.209 (0.6999)                                 | 3.494 (0.6139)                                 |
| Day 14 | n         | 23                                             | 25                                             | 24                                             |
|        | Mean (SD) | 3.767 (0.7144)                                 | 3.726 (1.1215)                                 | 3.396 (0.5913)                                 |
| Day 30 | n         | 4                                              | 0                                              | 0                                              |
|        | Mean (SD) | 4.595 (1.6351)                                 | 0                                              | 0                                              |
| Day 90 | n         | 4                                              | 0                                              | 0                                              |
|        | Mean (SD) | 3.870 (1.1655)                                 | 0                                              | 0                                              |

The repeated measurements are not taken into account for the calculation of the statistics