Pharmacokinetics of the monoclonal antibody MHAA4549A administered in combination with oseltamivir in patients hospitalized with severe influenza A infection

Rong Deng, Gaohong She, Mauricio Maia, Jeremy J. Lim, Melicent C. Peck, Jacqueline M. McBride, Priya Kulkarni, Priscilla Horn, Aide Castro, Elizabeth M. Newton, Jorge A. Tavel, William D. Hanley

SUPPLEMENTAL MATERIAL
Study Sites

1. CEPREP; Hospital Universitario, Hospital Universitario "Dr. Jose Eleuterio Gonzalez", Av. Francisco I. Madero y Gonzalitos s/n Col. Mitras Centro, 64460, Monterrey, Mexico
2. CHU UCL Mont-Godinne, Avenue Docteur Thérasse, 1, 5530, Yvoir, Belgium
3. UZ Leuven Gasthuisberg, Herestraat 49, 3000, Leuven, Belgium
4. Réanimation Polyvalente, CHU Limoges, 3 Avenue Martin Luther King, 87043, Limoges, France
5. Service de réanimation médicale, Hôpital Bretonneau, 2 Boulevard Tonnellé, 37044, Tours, France
6. Hopital Cochin University Hospital, 27 Rue du Faubourg Saint Jacques, 75679, Paris, France
7. 5th Multifunctional Hospital for Active treatment, 67A Stoletov Boulevard, 1233, Sofia, Bulgaria
8. UMCU, PO Box 85500, F02.126, 3508 GA, Utrecht, Netherlands
9. Ikazia Hospital, Montessoriweg 1, 3083 AN, Rotterdam, Netherlands
10. Isala, Dr. van Heesweg 2, Klinische, trial team, 8025 AB, Zwolle, Netherlands
11. Queen Elizabeth Hospital, Queen Elizabeth Hospital, Birmingham, B15 2th, United Kingdom
12. Mutua de Terrassa, Plaça Dr. Robert, 5, Medicina Intensiva, 4ª planta, 08221, Terrassa, Barcelona, Spain
13. Bellvitge University Hospital, Avda Feixa Llonga s/n Medi cina Intensiva, 1ª Planta, 08907, Barcelona, Barcelona, Spain
14. Servicio de Medicina Intensiva Hospital Universitario la Fe, Av Bulevar sn, 46026, Valencia, Spain
15. Hospital Universitari Vall d'Hebron, PG Vall D'Hebron 119-129, ICU, 08035, Barcelona, Barcelona, Spain
16. SHATPPD Dr. Dimitar Gramatikov, Ruse Ltd., 1 Aleya Lilia Str., 7002, Ruse, Bulgaria
17. Hospital Universitario San Cecilio, Avda Oloriz 16, 18012, Granada, Granada, Spain
18. Hospital Univ. de Getafe. Servicio de Neurologia, Carretera de Toledo kn 12, 5, Getafe, 28905, Madrid, Madrid, Spain
19. Hosp. Clinico San Carlos, C/Prof. Martin Lagos,s/n, 28040, Madrid, Madrid, Spain
20. Santa Casa de Misericordia; de Belo Horizonte, AV Francisco Sales 1111, 8 Andar - ALA-C-Santa Efígenia, 30150-221, Belo Horizonte, MG, Brazil
21. MHAT "Dr. Tota Venkova"- Gabrovo, 1 "Dr. Iliev- Detskia" Str., 5300, Gabrovo, Bulgaria
22. University Hospital Ostrava, Clinic of Infectious Medicine, 17. listopadu 1790, 708 52, Ostrava, Czech Republic
23. Service de Réanimation médicale - Bocage Central, 14 rue Paul Gaffarel BP77908, 21079, Dijon, France
24. Korea University Anam Hospital, 73 Inchon-ro, Seongbuk-Gu, 136-705, Seoul, Korea, Republic Of
25. PUC Campinas, Hospital de Maternidade Celso Pierro PUC Campinas, Av. John Boyd Dunlop, s/n - Pesquisa Clinica, Jardim Ipaussurama, 13060-904, Campinas, SP, Brazil
26. Military Medical Academy- MHAT, 3, Georgi Sofiiski Blvd., 1606, Sofia, Bulgaria
27. Municipal Healthcare Institution "City Hospital No. 2", Polygraphyeshkaya street, 1, 413124, Engels, Russian Federation
28. Municipal Clinical Hospital #8, 28, Gorkogo str., 454071, Chelyabinsk, Russian Federation
29. Réanimation médicale NHC, 1 place de l'hôpital, 67000, Strasbourg, France
30. FUNFARME, Av Brigadeiro Faria Lima, 5544, 15090000, Sao Jose Do Rio Preto, Sp, Brazil
31. FUNFARME, Fundação Faculdade Regional de Medicina de São José do Rio Preto/ Hospital de Base de São José do Rio Preto, Avenida Brigadeiro Faria Lima, 5544, 2 andar, 15090-000, Sao Jose do Rio Preto, SP, Brazil
32. Hospital Sao Vicente de Paulo, Rua Teixeira Soares, 808, 99010-080, Passo Fundo, RS, Brazil
33. CH Victor Dupouy, 69 rue du Lieutenant Colonel Prudhon Cedex, 95107, Argenteuil, France
34. Christchurch Hospital, Infectious Diseases Dept, Christchurch Hospital, Riccarton Ave, 8140, Christchurch, New Zealand
35. Hospital General de Tijuana, Av. Centenario # 1085, Zona Rio, 22320, Tijuana, Mexico
36. Hospital Clinic, Calle Villaroeil 170, Escalera 6-8, 2ª planta, 08036, Barcelona, Barcelona, Spain
37. Ottawa Hospital Research Institute, G12-50 Smyth Rd, K1H8L6, Ottawa, Ontario, Canada
38. Hospital de Mataro, Ctra Cirera, S/N, 08304, Mataro, Cantabria, Spain
39. King College Hospital NHS Foundation Trust, Denmark Hill, London, SE5 9RS, United Kingdom
40. Sahlgrenska Universitetssjukhuset, Department of Infectious Diseases - Sahlgrenska University Hospital, East Journalvägen 10, 416 85, Göteborg, Sweden
41. Uppsala University Hospital, Department of Infectious Diseases, Uppsala University hospital, 751 85, Uppsala, Sweden
42. The University Hospital Brno, Jihlavská 20, 625 00, Brno, Czech Republic
43. Hospital Nacional Adolfo Guevara Velasco, Avenida Anselmo Alvarez s/n, 84, Cuzco, Peru
44. CHD Vendée, Les Oudairies, Bd Stephane Moreau, 85925, La Roche Sur Yon, France
45. Skånes Universitetssjukhus, Verksamhetsområde Infektionssjukdomar, Ruth Lundskogsgata 3, 205 02, Malmö, Sweden
46. LHSC - University Hospital; Research Pharmacy, 268 Grosvenor Street, N6A 4V2, London, Ontario, Canada
47. Foothills Medical Centre, 3134 Hospital Drive Northwest, T2N 2T9, Calgary, Alberta, Canada
48. Foothills Medical Centre, 3280 Hospital Drive, T2N 4Z6, Calgary, Alberta, Canada
49. Toronto East General, 825 Coxwell Ave, D-306, M4C 3E7, Toronto, Ontario, Canada
50. Moncton Hospital, 135 Macbeath Avenue, E1C 6Z8, Moncton, New Brunswick, Canada
51. Ziv Medical Center, POB 1008, 13100, Safed, Israel
52. Nazareth EMMS Hospital, P.O. Box 11, 16100, Nazareth, Israel
53. Tel-Aviv Sourasky Medical Center, 6 Weitzman Street, 6423906, Tel Aviv, Israel
54. Hadassit Medical Research Services and Development Ltd, Kiryat Hadassah, 91120, Jerusalem, Israel
55. Soroka University Medical Centre, Post Office Box 151, 84101, Beer Sheva, Israel
56. Galilee Medical Center, Rambam Road, 13100, Safed, Israel
57. Hospital del Mar, Passeig Maritim, 25-29, 08003, Barcelona, Barcelona, Spain
58. Peter Lougheed Centre, 3500 26th Avenue Northeast, T1Y 6J4, Calgary, Alberta, Canada
59. University Multiprofile Hospital for Active Treatment and Emergency Medicine N. I. Pirogov EAD, 21 Totleben Boulevard, 1606, Sofia, Bulgaria
60. Multiprofile District Hospital for Active Treatment Dr. Stefan Cherkezov AD, 2, Buzludzha Str., 5000, Veliko Tarnovo, Bulgaria
61. Kyiv City Clinical Hospital #4, 17, Solomianska str., 03110, Kyiv, Ukraine
62. Hospital Universitario Son Espases, 2 Plein Laan, 1090, Brussel, Barcelona, Spain
63. Kyiv City Clinical Hospital #9, 1 Ryzhskia str., 04060, Kyiv, Ukraine
64. CHRU Lille, 2, Avenue Oscar Lambret, 59037, Lille Cedex, France
65. Wanfang Hospital, No.111 Section 3 Hsing-long Road, 116, Taipei, Taiwan
66. Kaohsiung Medical University Hospital, Cancer Center, No.100, Tzyou 1st Rd., 807, Kaohsiung, Taiwan
67. Hospital Civil de Guadalajara Fray Antonio Alcalde, Calle Hospital 278, Colonia El Retiro, 44280, Guadalajara, Mexico
68. CHRU Nancy, 29 Avenue du Maréchal de Lattre de Tassigny, 54000, Nancy, France
69. Rockyview General Hospital, 3134 Hospital Drive Northwest, T2N 2T9, Calgary, Alberta, Canada
70. Chaim Sheba Medical Center, Tel-Hashomer 52621, 52621, Ramat Gan, Israel
Fig. S1. Study flow indicating MHAA4549A and OS dosing, discontinuations, and PK-evaluable population. OS, oseltamivir.

| Step | Description |
|------|-------------|
| 1    | 324 patients assessed for eligibility |
| 2    | 156 ineligible |
| 3    | 168 enrolled |
| 4    | 2 randomization errors |
| 5    | 166 randomized |
| 6    | 8 did not receive treatment |
|      | 3 did not meet eligibility |
|      | 2 withdrew consent |
|      | 2 no drug available |
|      | 1 no randomization date; drug not ready |
| 7    | 56 assigned placebo + OS |
|      | 10 received 150-mg OS |
|      | 40 received 75-mg OS |
|      | 5 received 30-mg OS |
|      | 1 received 10-mg OS |
| 8    | 55 assigned 3600-mg MHAA4549A + OS |
|      | 9 received 150-mg OS |
|      | 42 received 75-mg OS |
|      | 4 received 30-mg OS |
| 9    | 47 assigned 8400-mg MHAA4549A + OS |
|      | 3 received 150-mg OS |
|      | 39 received 75-mg OS |
|      | 5 received 30-mg OS |
| 10   | 9 discontinued study |
|      | 4 deaths |
|      | 2 lost to follow-up |
|      | 3 withdrawal by subject |
| 11   | 13 discontinued study |
|      | 6 deaths |
|      | 2 lost to follow-up |
|      | 3 withdrawal by subject |
|      | 2 other |
| 12   | PK-evaluable population: 56 for OS |
|      | 0 for MHAA4549A |
| 13   | PK-evaluable population: 55 for OS |
|      | 55 for MHAA4549A |
| 14   | PK-evaluable population: 47 for OS |
|      | 47 for MHAA4549A |
| 15   | 8 did not receive treatment |
|      | 3 did not meet eligibility |
|      | 2 withdrew consent |
|      | 2 no drug available |
|      | 1 no randomization date; drug not ready |
| 16   | 9 discontinued study |
|      | 4 deaths |
|      | 2 lost to follow-up |
|      | 1 withdrawal by subject |
|      | 2 other |
| 17   | PK-evaluable population: 56 for OS |
|      | 0 for MHAA4549A |
| 18   | PK-evaluable population: 55 for OS |
|      | 55 for MHAA4549A |
| 19   | PK-evaluable population: 47 for OS |
|      | 47 for MHAA4549A |

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**Notes:**
- **OS**: oseltamivir
- **PK-evaluable population** indicates patients who had evaluable pharmacokinetic data.

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**Legend for abbreviations:**
- **MHAA4549A**: A hypothetical antiviral drug
- **OS**: Oseltamivir, a neuraminidase inhibitor used in the treatment of influenza
Fig. S2. Dose-normalized MHAA4549A serum concentration-time profiles. Data are mean + SD. SD, standard deviation.
**Fig. S3.** Observed (red) versus simulated (blue) NP $C_{\text{max}}$ from a semi-quantitative PK model.\textsuperscript{18} Box plots indicate the median (heavy bar) and interquartile range (boxes, IQR=25\textsuperscript{th}–75\textsuperscript{th} percentiles); the upper whisker extends from hinge to highest value within 1.5 times IQR of hinge; the lower whisker extends from hinge to lowest value within 1.5 times IQR of hinge. $C_{\text{max}}$, maximum serum concentration; IQR, interquartile range; NP, nasopharyngeal.