Ampligen (Poly I:Poly C12U) as a potential COVID-19 treatment: safety and tolerability of repeated intranasal administration in healthy subjects

Johan L. van der Plas[1,2], Lisanne C.A. Smidt[1], Aliede E. in 't Veld[1], Christina Yfanti[1], Ingrid M.C. Kamerling[1,2], Naomi B. Klarenbeek[1,3], Diane L. Young[4], David R. Strayer[4], Manon A.A. Jansen[1], Matthijs Moerland[1]

[1]Centre for Human Drug Research, Leiden, the Netherlands. [2]Department of Infectious Diseases, Leiden University Medical Center, Leiden, the Netherlands. [3]Department of Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands . [4]AIM ImmunoTech Inc., Ocala, Florida, United States.

Introduction

Rintatolimod (Ampligen®) is a synthetic double-stranded RNA (Poly I: Poly C12U) and acts as a selective Toll-like receptor 3 agonist. Therefore, rintatolimod can mimick antiviral immune responses by the induction of type 1 interferons. In addition, antiviral activity of rintatolimod against coronaviruses (incl SARS-CoV-2) has been shown in preclinical studies. Intranasal administration of rintatolimod has the potential to be used as a prophylactic or early treatment against COVID-19 and other respiratory viral infections by acting at the point of virus entry. Here we present data of a phase I trial investigating repeated dosing regimens of intranasal rintatolimod.

Aim

To assess the safety, tolerability and biological activity of repeated intranasal administration of rintatolimod

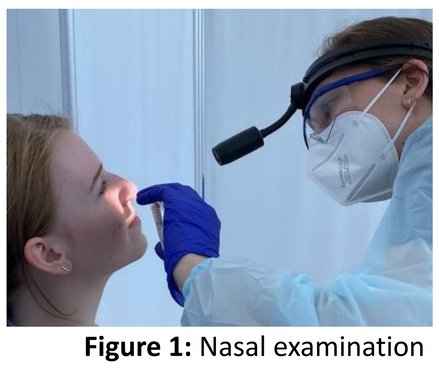

Figure 1: Nasal examination

Methods

Study design

- Randomized, double blind, placebo-controlled, dose-escalation study
- Rintatolimod or placebo (4:1) administered intranasally every other day (q.o.d) for a period of 13 days (7 doses)
- Study population: healthy male and female subjects (age 18-70 yrs).

Safety and tolerability outcomes

- Frequency and severity of adverse events (AE), including solicited local AEs (e.g. upper respiratory complaints), change in vital signs, laboratory values, physical examination, nasal pain and integrity of nasal mucosa (Figure 1)

Pharmacodynamic outcomes (Table 1)

- Mucosal lining cytokines (type I interferons and NFκB-mediated cytokines)
- Mucosal immune cell characterization by flow cytometry (granulocytes, T cells, B cells, dendritic cells, macrophages/monocytes)

Table 2: Possibly and probably treatment-related AEs in exposed subjects

Adverse events			Rintatolimod dose administered 75ug	200 ug	500 ug	1250 ug	Total (all 4 dose levels)
			Number of AEs (in % of subjects)				
Relatedness		**Probable**	**-**	**-**	**6 (25%)**	**1 (13%)**	**7 (9%)**
	Severity	Mild	-	-	6 (25%)	1 (13%)	7 (9%)
	Severity	Moderate	-	-	-	-	-
	Severity	Severe	-	-	-	-	-
		Possible	**3 (38%)**	**5 (50%)**	**4 (25%)**	**6 (50%)**	**18 (41%)**
	Severity	Mild	3 (38%)	5 (50%)	4 (25%)	5 (50%)	17 (41%)
	Severity	Moderate	-	-	-	1 (13%)	1 (3%)
	Severity	Severe	-	-	-	-	-
		Total	**3 (38%)**	**5 (50%)**	**10 (38%)**	**7 (50%)**	**25 (44%)**

Figure 2: Consort flow diagram

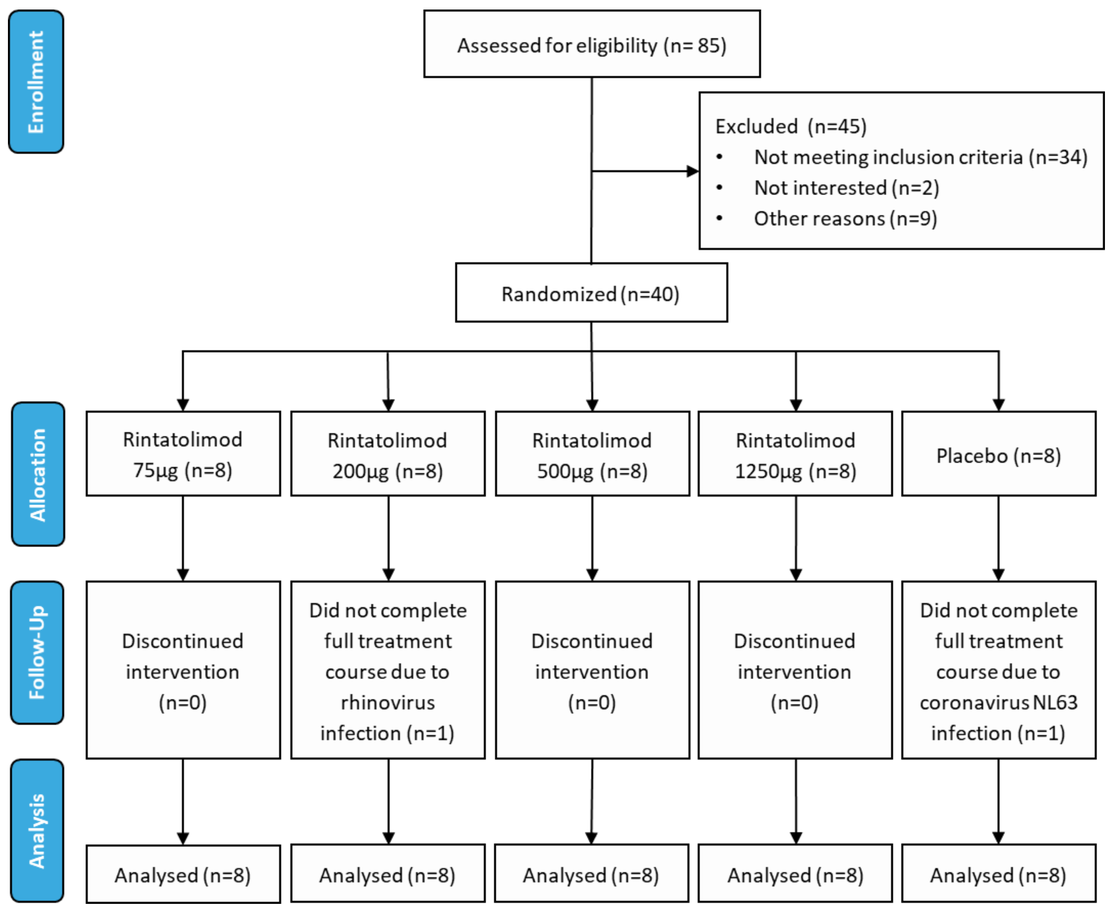

Table 1: Schedule of dosing regimen and characterization of biological activity

	Treatment period													
Time / Activity	Day 1			Day 2	Day 3	Day 5	Day 7	Day 9	Day 11	Day 13			Day 14	Day 15
	0h	3h	6h							0h	3h	6h		
Intranasal administration	x				x	x	x	x	x	x				
Mucosal immune cells[1]	x[3]		x	x	x		x		x	x		x	x	x
Mucosal lining fluid[2]	x[3]	x	x	x	x		x		x	x	x	x	x	x

[1]Sampling performed by nasal scrape; [2]Sampling performed by nasosorption; [3]pre-dose.

Results

- 40 subjects included (Figure 2)
- No safety or tolerability findings of clinical concern or dose limiting toxicities observed.
- Adverse events only mild-to-moderate (Table 2)
- No severe or serious adverse events reported
- Pharmacodynamic analysis expected in the coming months.

Conclusions

- Repeated intranasal administration of 7 rintatolimod doses q.o.d. was well tolerated in all tested dose levels.
- Further research of rintatolimod as prophylactic or early treatment for COVID-19 in patients is warranted.

Centre for Human Drug Research | Zernikedreef 8 | 2333 CL Leiden | The Netherlands | Tel +31 71 52 46 400 | info@chdr.nl | www.chdr.nl