8th European Immunology Conference
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Theme: Disseminating the New Trends in Immunology

Released-active antibodies are innovative products for the effective management of severe respiratory viral infections

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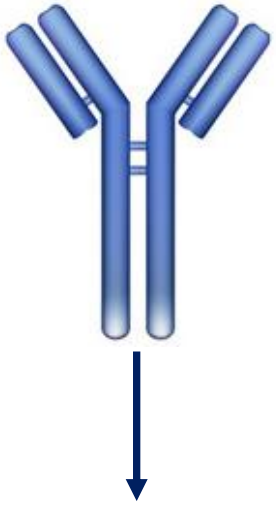
INTRODUCTION

Antibodies-based drugs are broadly studied and used

49 **Europe**[1]



52 **USA**[1]

Application:

Autoimmune diseases; Cardiovascular diseases; Infectious diseases; Cancer; Inflammation[2]

Limitations[3]**:**

- Production
- Cost
- Pharmacokinetics
- Route of administration
- Safety

Approaches[2]**:**

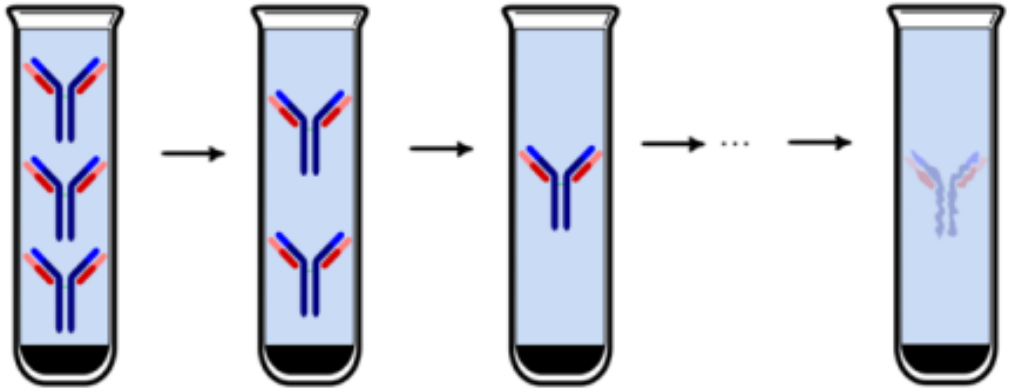
- Adjuvants
- Modification
- Encapsulation

1 – *Reichert J.M., updated October 23, 2016 (http://antibodysociety.org);* 2 – Chames P. et al. *Br J of Pharmacol* 157: 220-233 (2009); 3 – Zhang M.-Y. et al. *BioMed Research International* 2015, ID 168935 (2015)

BIOTECHNOLOGICAL PLATFORM

Technology of concentration reduction

Therapeutic Antibodies



Released-active form of antibodies

Specific action
+
Neutralize the target

Specific action
+
Modify the target

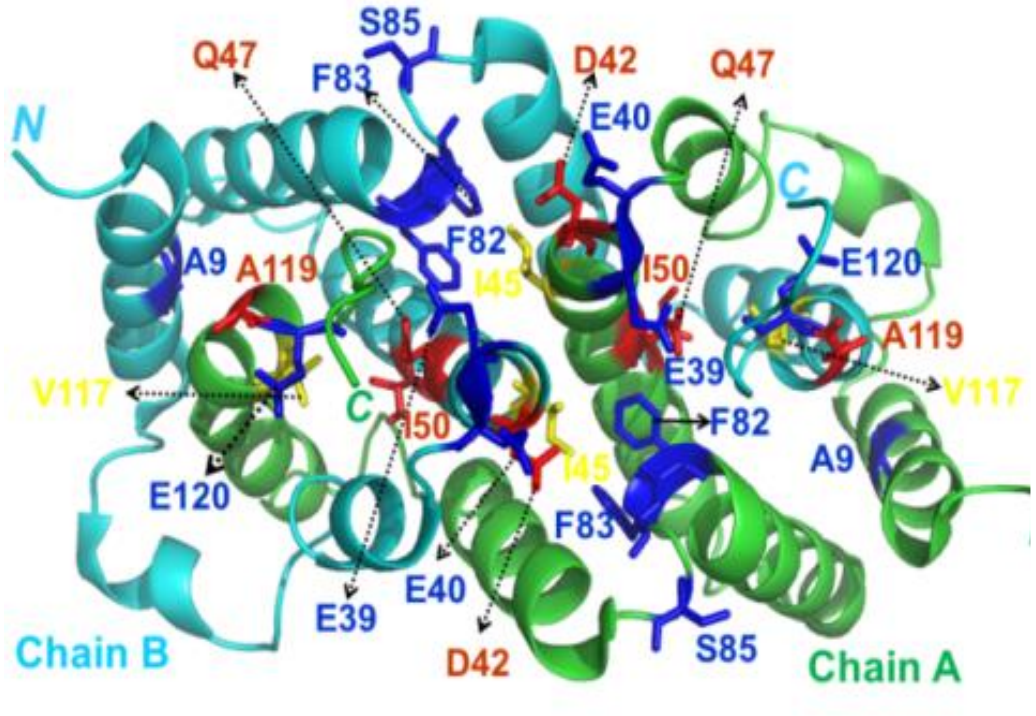
Released-activity determined by initial substance derivatives' emergence

Epstein O.I. *Usp Fiziol Nauk* 44:54-76 (2013)

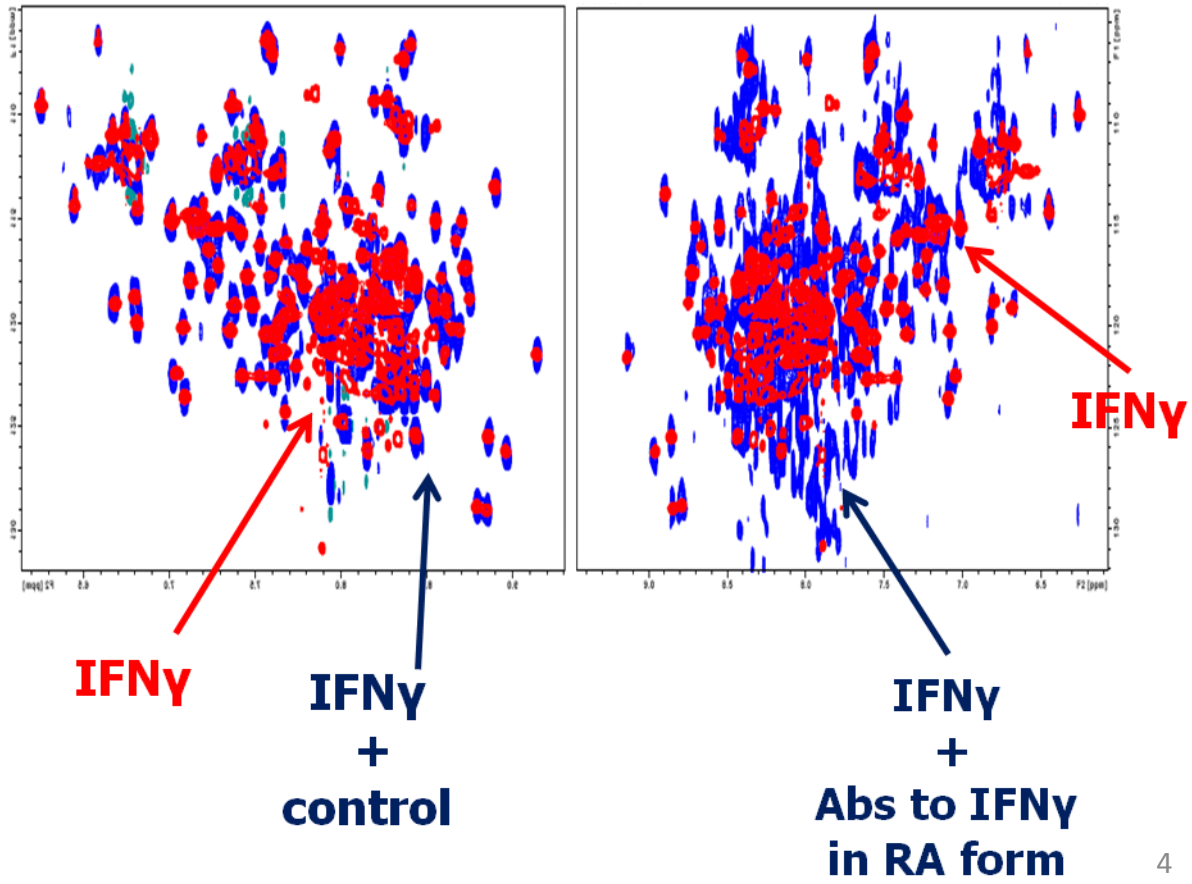
TARGET MODIFICATION

Abs to IFNγ in RA form induces conformation changes of the IFNγ

Model: Nuclear Magnetic Resonance Spectroscopy



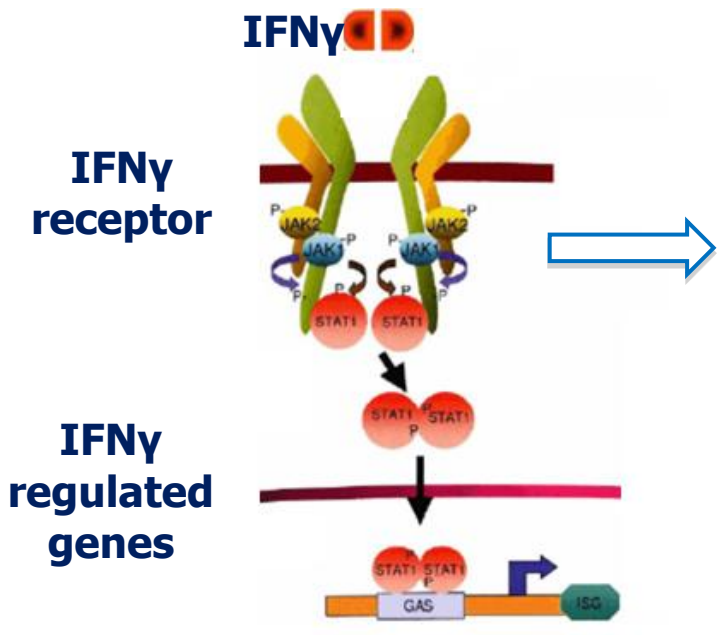
2-Dimension NMR-spectrum of IFNγ molecule



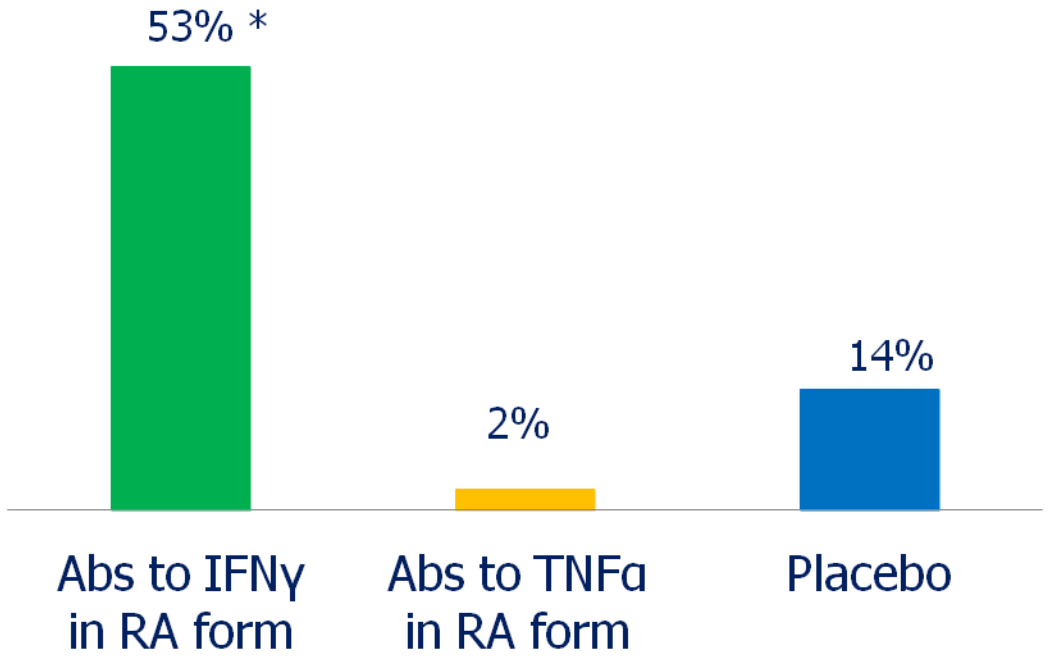
TARGET MODIFICATION

Abs to IFNγ in RA form enhance ligand-receptor interaction

Model: radioligand binding assay



Specific binding of [^{125}I]IFNγ with IFNγ receptor, % vs control



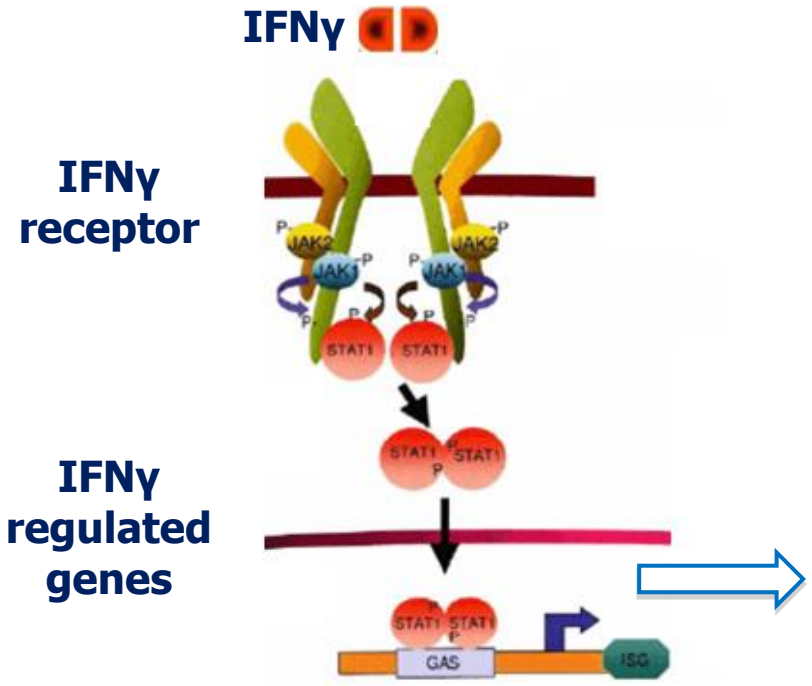
Picture was adapted from:
"The Interferons: Characterization and Application"
(Ed. By A. Meager) 2006 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

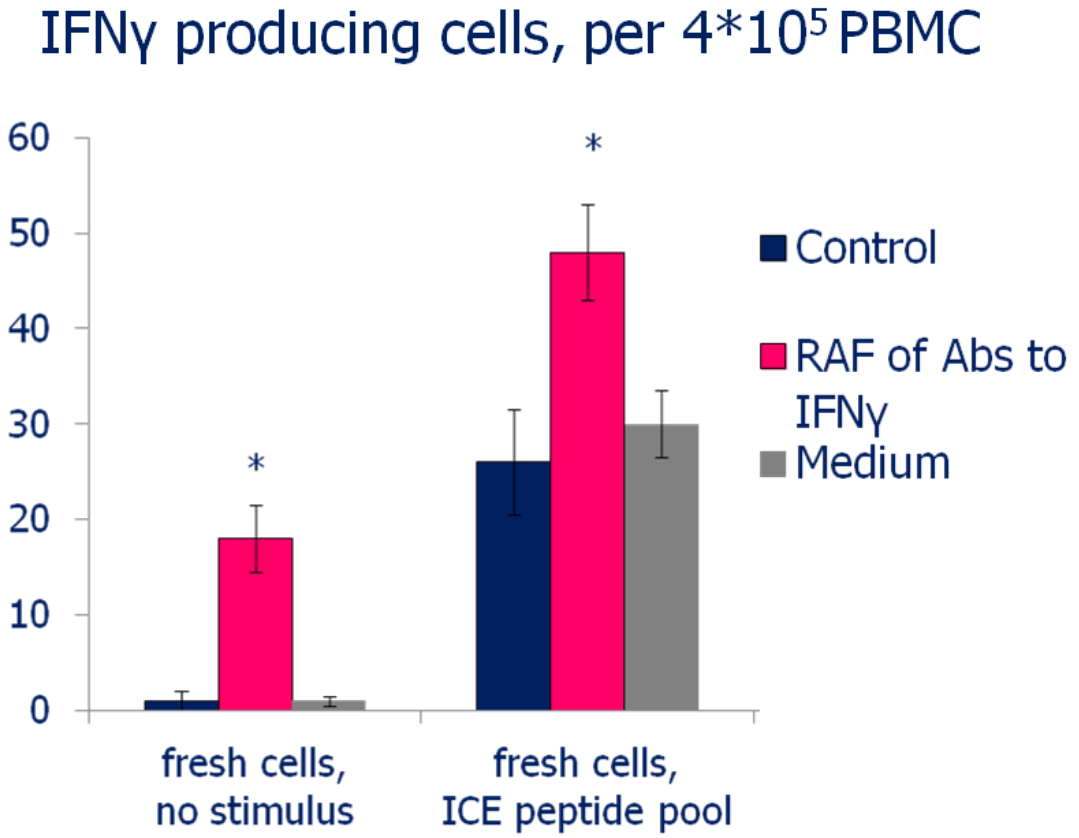
**- p<0.05 vs Abs to TNFa in RA form, placebo*

MODIFICATION OF BIOLOGICAL PATHWAYS

Abs to IFNγ in RA form increase the number of IFNγ producing cells

Model: production of IFNγ by PBMC *in vitro*





* - $p<0.05$ *vs* control

Picture was adapted from:
"The Interferons: Characterization and Application"
(Ed. By A. Meager) 2006 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

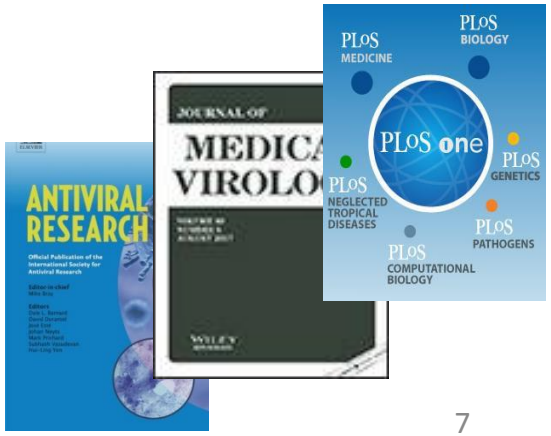
ABS IN RA FORM: FIRST ANTIVIRAL PRODUCT

Anaferon
Abs to IFNγ in RA form

Launched in 2001-2002
Registered in 17 countries

The most prescribed pediatric medicine in Russia (2012)
Brand №1 in Russia 2013 prize in antiviral medicines

Publications in peer-reviewed Russian and international journals

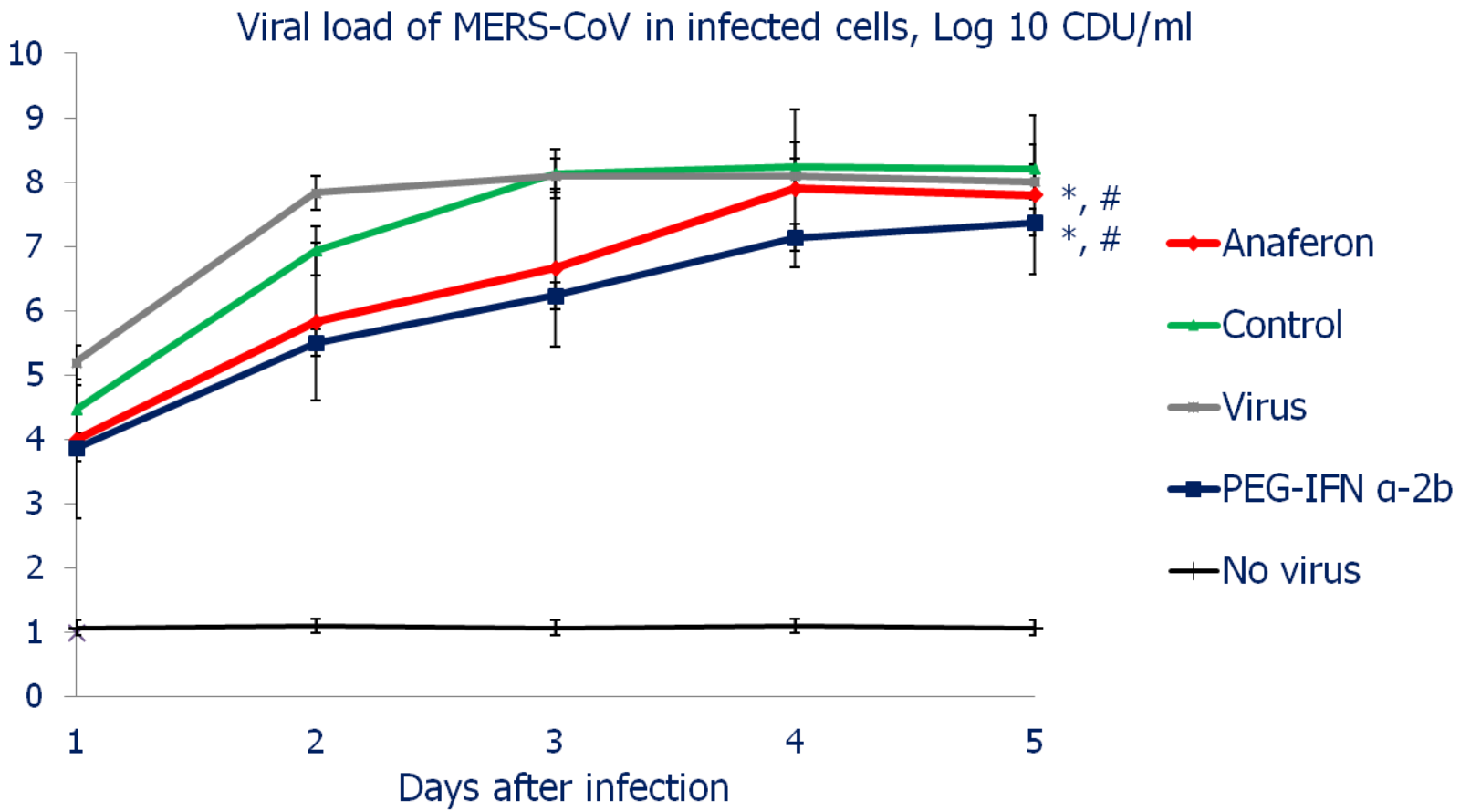


Middle East Respiratory Syndrome Coronavirus

Target: IFNγ

Agent: Abs to IFNγ in RA form

Anaferon is effective in treatment of MERS-CoV infection



*, #- p<0.05 vs PEG-IFN α-2b-treated group, virus control

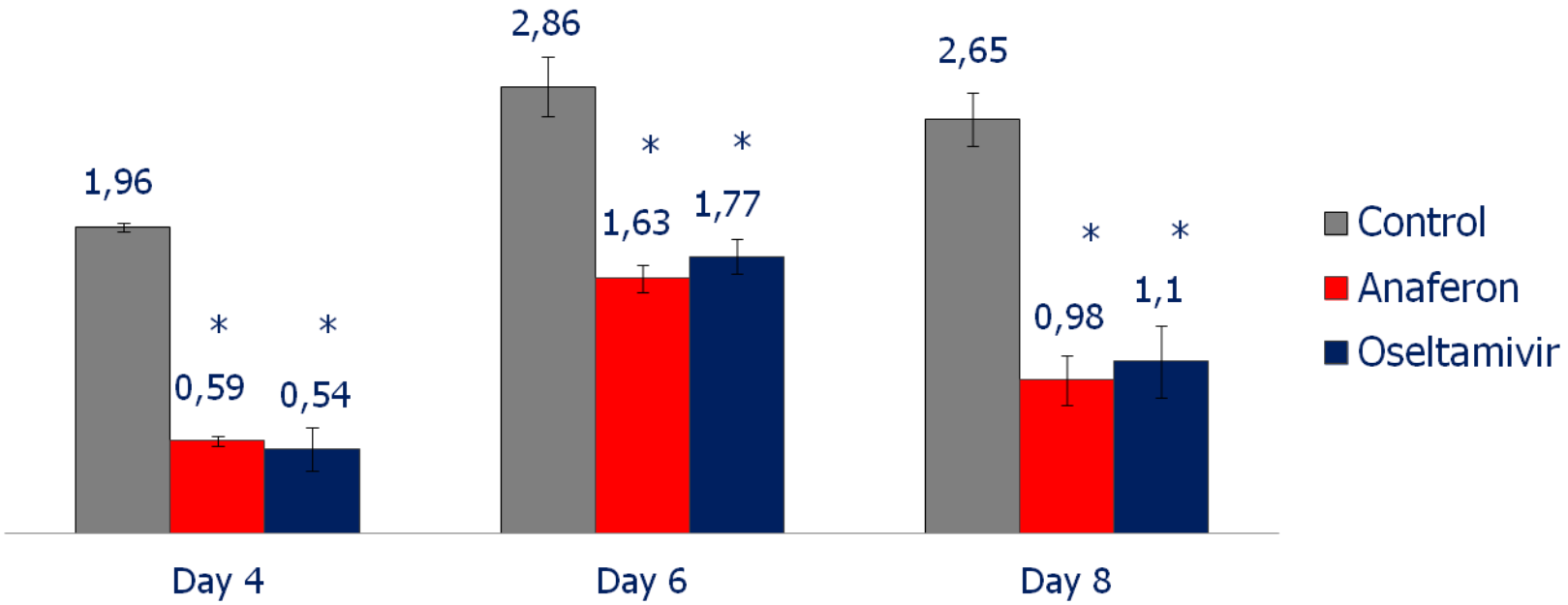
INFLUENZA

Target: IFNγ

Agent: Abs to IFNγ in RA form

Anaferon is effective against pandemic influenza strain H1N1

Viral load in lungs of mice inoculated with ID_{100} Influenza virus A/California/07/2009 (H1N1)v, log $TCID_{50}$/ml



* - p<0.05 vs control

INFLUENZA

Target: IFNγ

Anaferon is effective against 'swine flu' (A/H1N1)

Agent: Abs to IFNγ in RA form

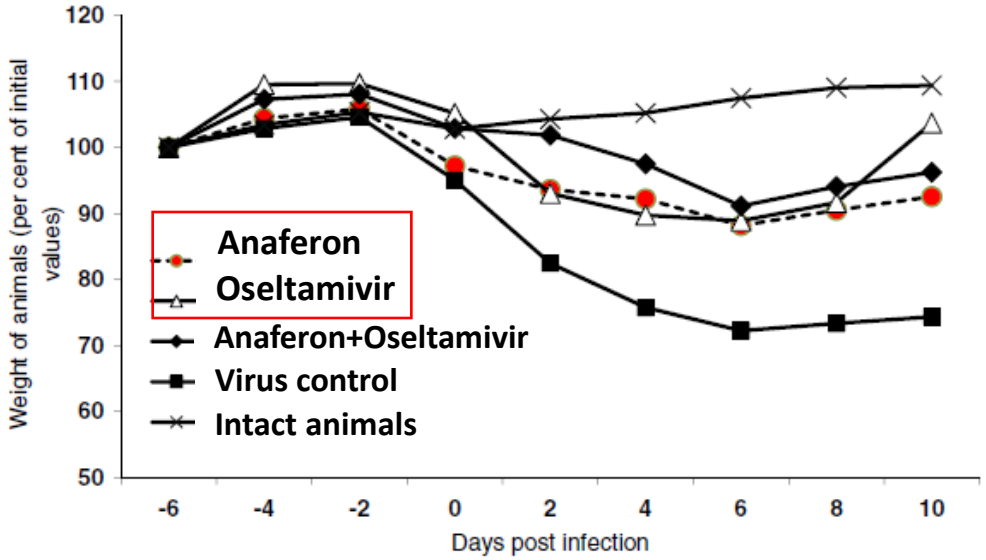


Fig. 1. Dynamics of body weight of mice in the course of pneumonia caused by influenza virus A/California/7/09 (H1N1)v.

Table 1
Protective activity of AC® against influenza A(H1N1)2009-caused lethal pneumonia in BALB/c mice. When $P < 0.05$ values are indicated in bold.

Treatment	Virus dose	Survival/total(% survival)	Mean day to death ± SEM	Index of protection (%)	Lung data	
					Virus titer ($log_{10}EID_{50}$/20 mg tissue ± SEM)	Medium size of foci of pneumonia (%)
AC®	**1 LD50**	**7/20 35%**	20.1 ± 0.9*	89.5	5.1 ± 0.9*	17.2 ± 4.7*
			11.3 ± 1.7	25.7	nd[a]	nd[a]
Oseltamivir(20 mg/kg/day)	**10 LD50**	**2/20 10%**	19.7 ± 0.9*	78.9	3.4 ± 0.6*	9.2 ± 3.0*
			7.9 ± 1.0	-2.9	nd[a]	nd[a]
AC® + Oseltamivir(20 mg/kg/day)	1 LD_{50}	**10/20 50%**	20.9 ± 0.1*	89.5	3.1 ± 1.2*	16.5 ± 4.5*
	10 LD_{50}		13.3 ± 1.8*	42.9	nd[a]	nd[a]
Control(no treatment)	1 LD_{50}	21/40 (52.5%)	15.8 ± 0.9	0	6.3 ± 0.4	34.5 ± 4.6
	10 LD_{50}	5/40 (12.5%)	7.9 ± 0.9	0	nd[a]	nd[a]
Uninfected(no treatment)	0	10/10 (100%)	–	–	–	–

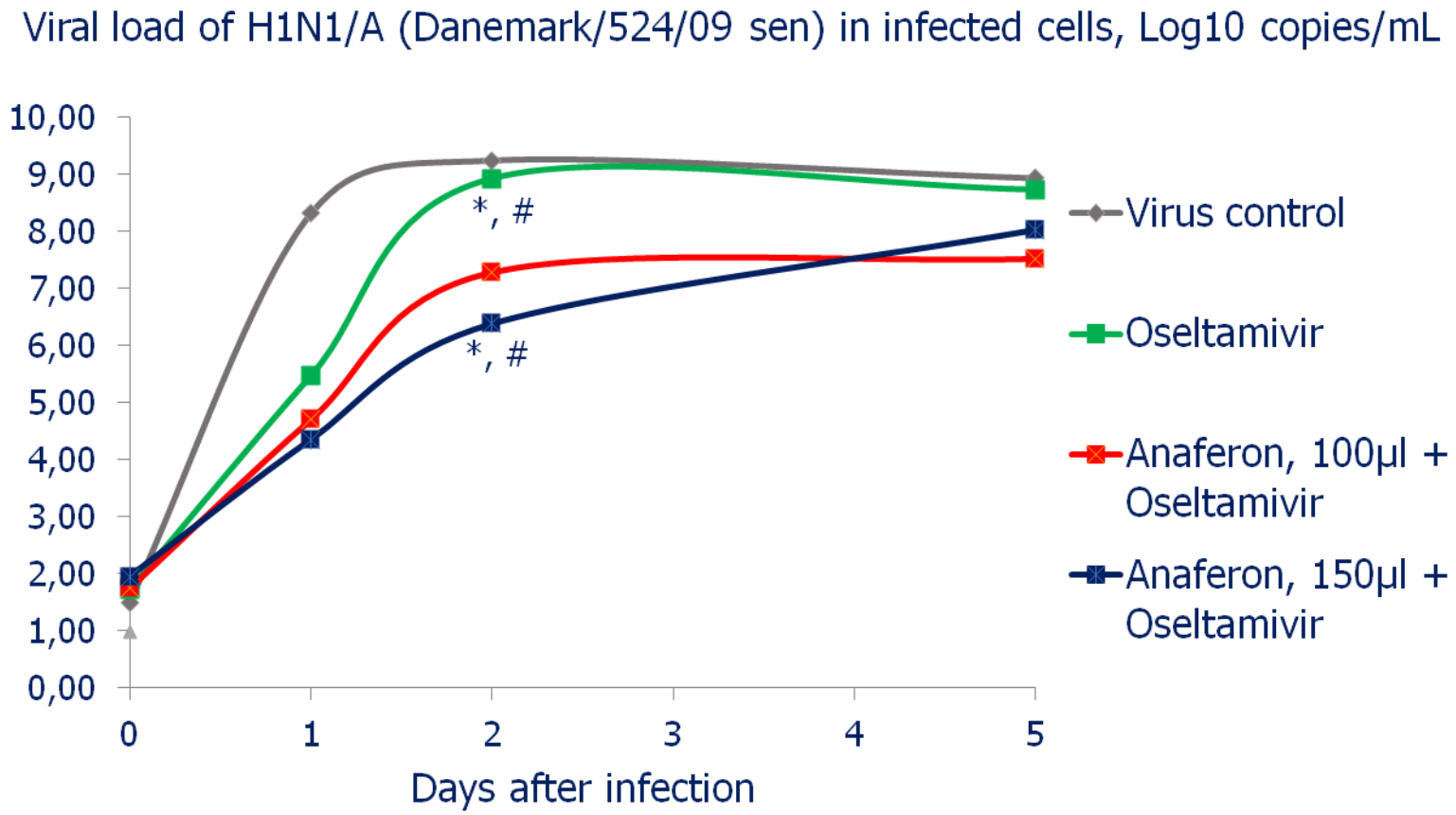
Tarasov S.A. et al. *Antiviral Res* 93:219-224 (2012)

INFLUENZA

Target: IFNγ

Agent: Abs to IFNγ in RA form

Anaferon increases the efficacy of Oseltamivir in treatment of Oseltamivir-sensitive strain of Influenza virus (A/H1N1pdm09)



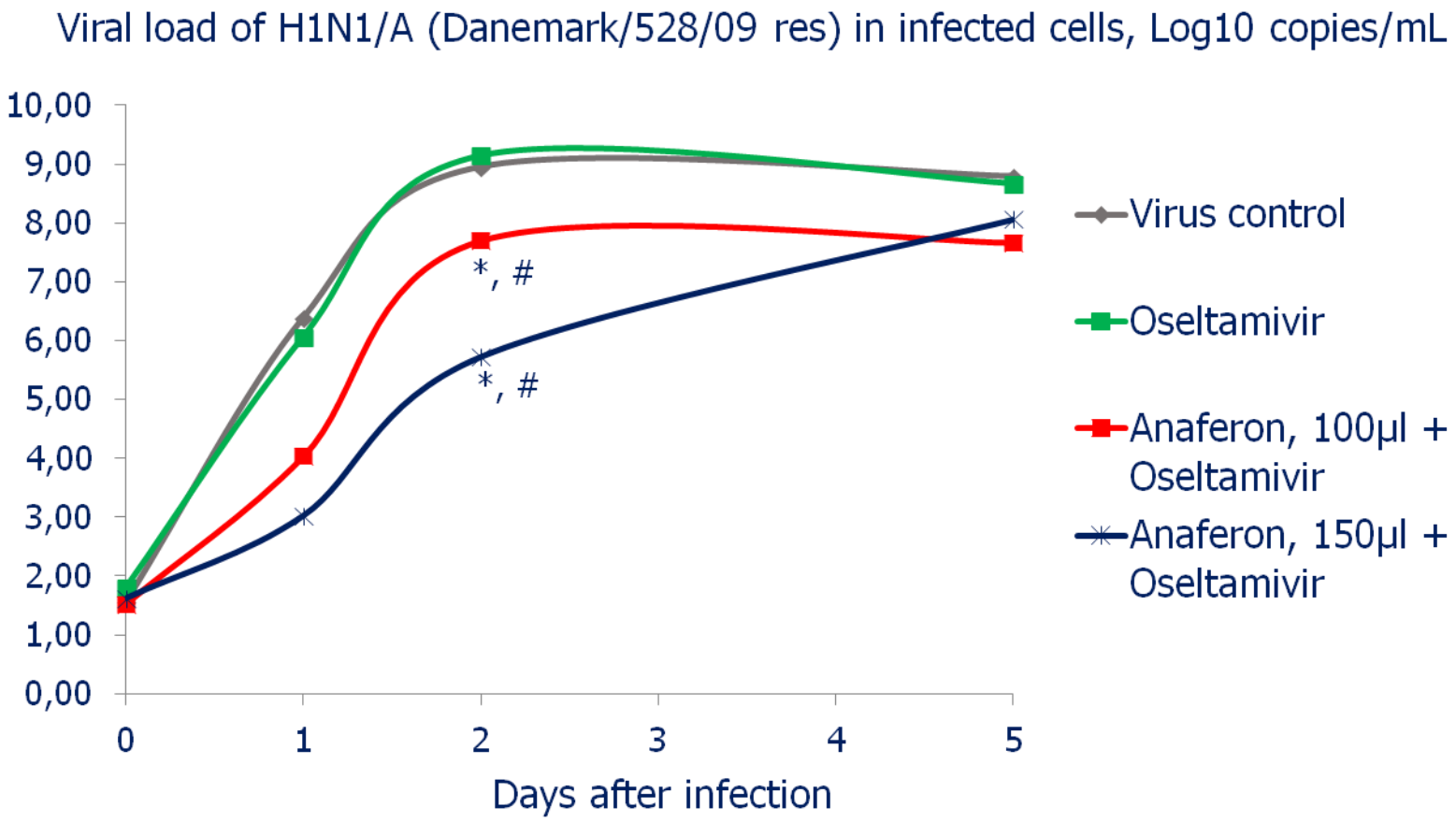
*, #- p<0.05 vs Oseltamivir-treated group, virus control

INFLUENZA

Target: IFNγ

Agent: Abs to IFNγ in RA form

Anaferon is effective in treatment of Oseltamivir-resistant strain of Influenza virus (A/H1N1pdm09)



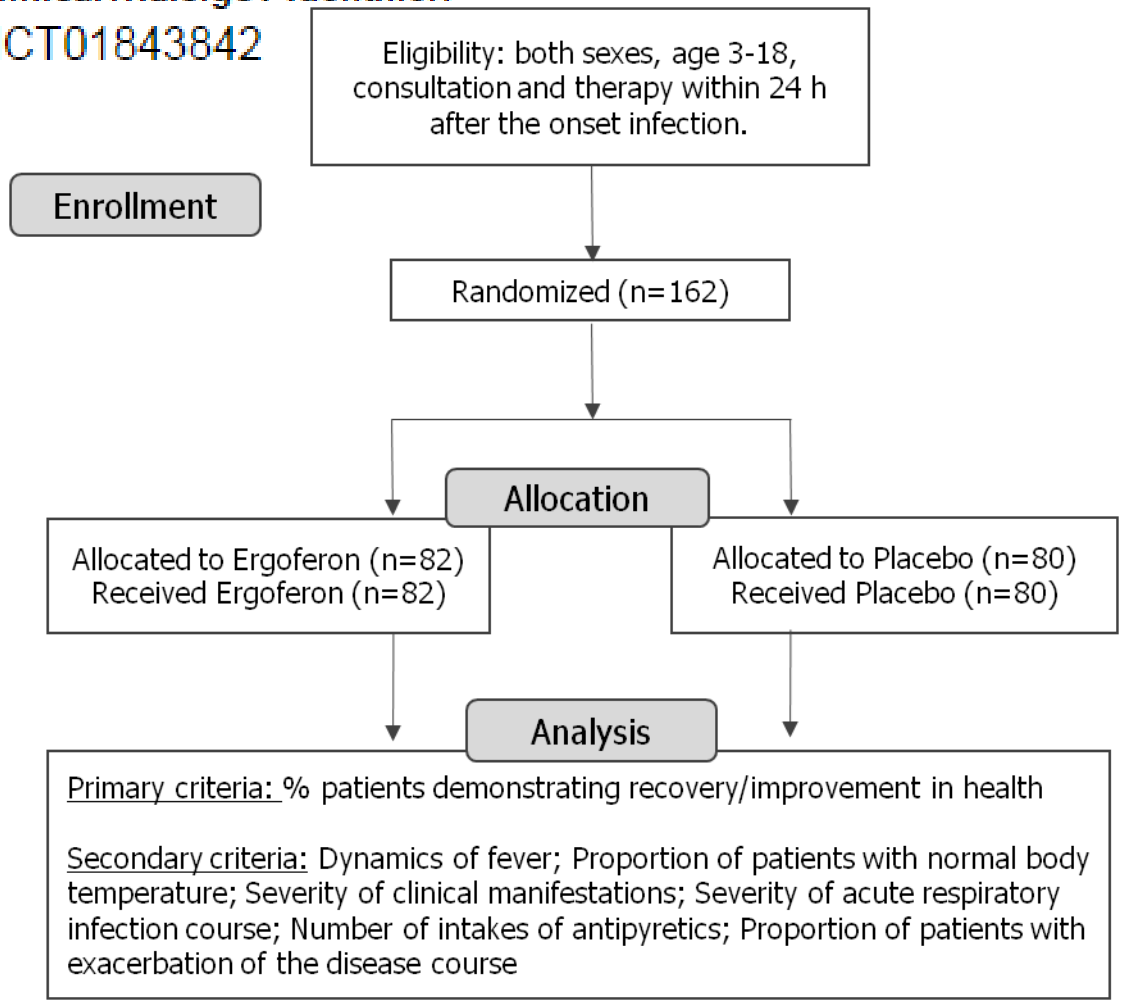
*, #- p<0.05 vs Oseltamivir-treated group, virus control

EFFICACY IN CLINICS

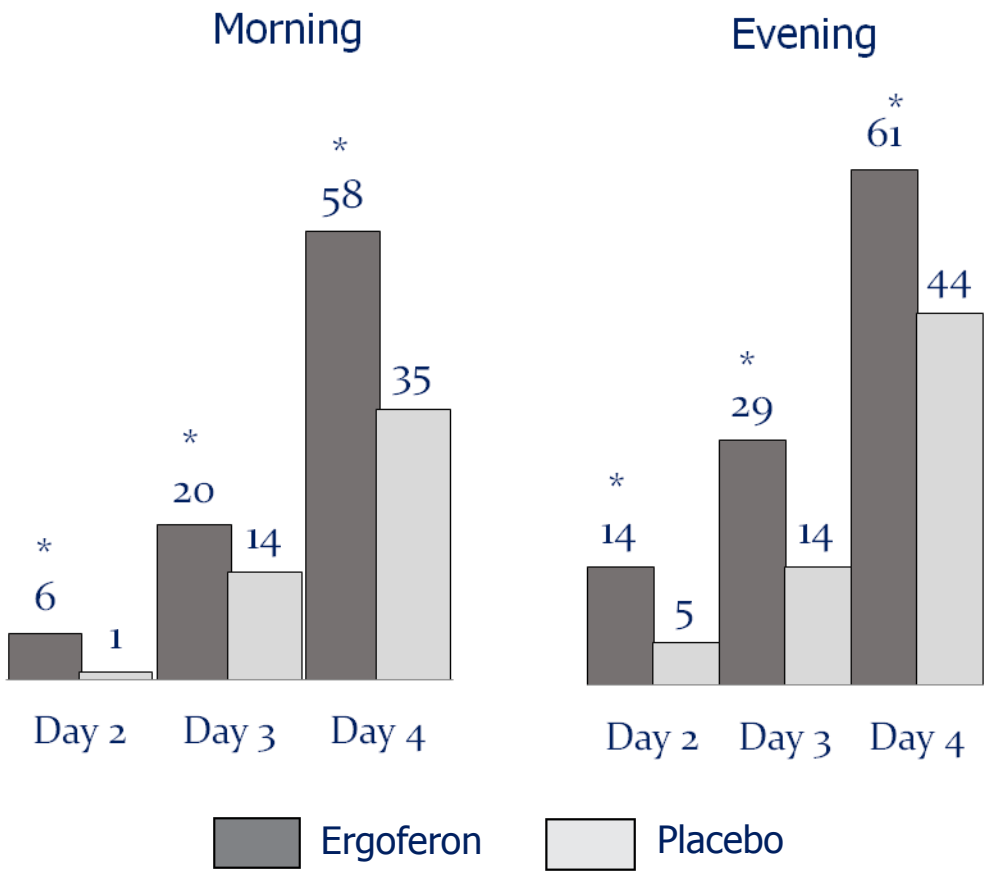
Ergoferon proven clinical efficacy by randomized double blind placebo control trials

ClinicalTrials.gov

ClinicalTrials.gov Identifier:
NCT01843842



Percentage of patients with recovery/improvement in health



* - p<0.05 vs placebo

Geppe N.A. et. al. *Antibiotics and Chemotherapy*, 2014, 59: 5-6

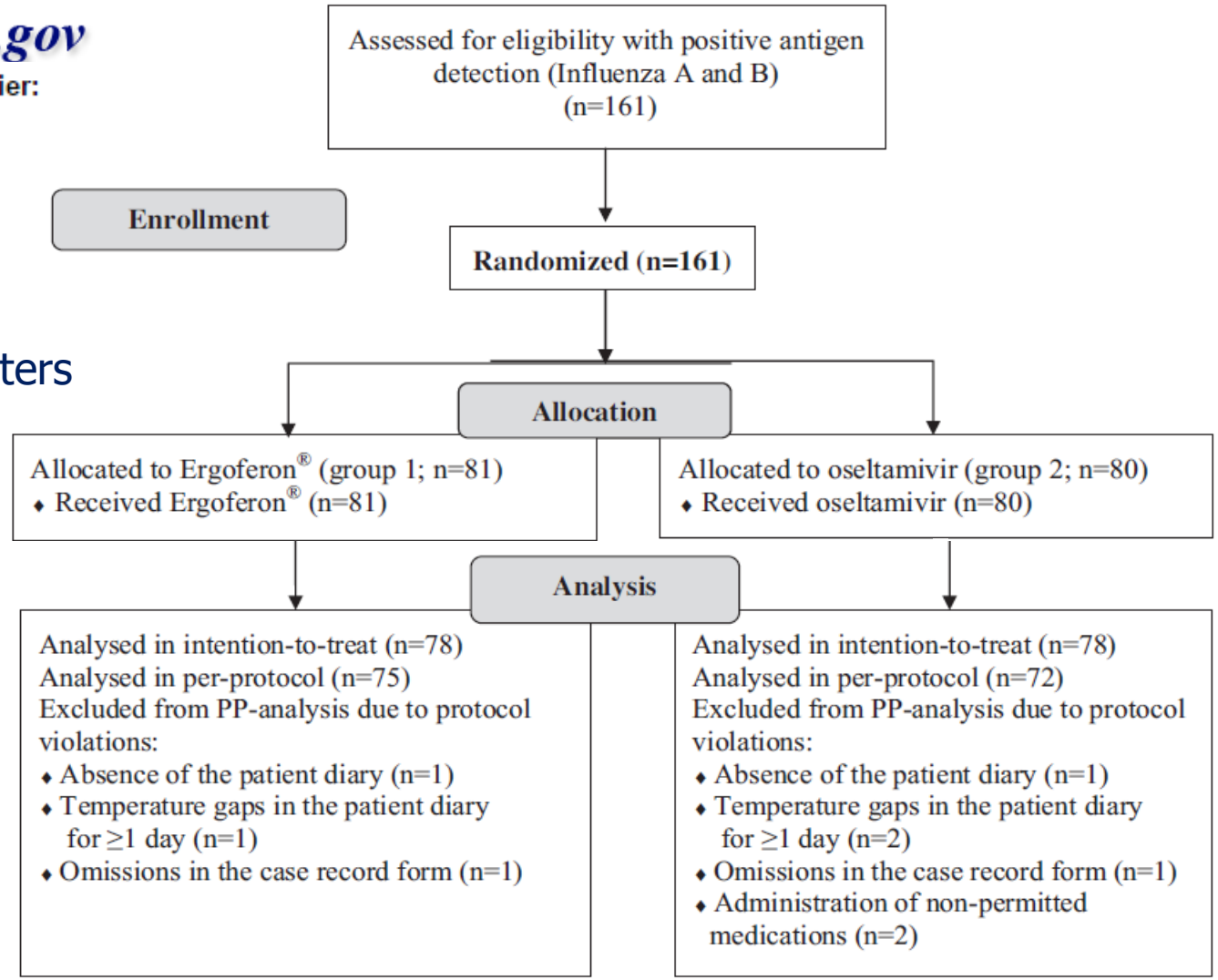
EFFICACY IN CLINICS

Ergoferon proven clinical efficacy comparable to Oseltamivir by multicenter open-label randomized trials

ClinicalTrials.gov

ClinicalTrials.gov Identifier:
NCT01804946

Study design:
- Both sexes
- age 18-60
- 12 research centers



Rafalsky V. et. al. *International Journal of Infectious disease*, 2016, 51: 47-55

EFFICACY IN CLINICS

Ergoferon proven clinical efficacy comparable to Oseltamivir by multicenter open-label randomized trials

Duration of fever and time to treatment-associated resolution of influenza symptoms[a]

Symptom	Duration of symptoms, days		
	ITT analysis		
	Group 1 ($n=78$)	Group 2 ($n=78$)	Statistics[b]
Fever	2.1 ± 1.5	2.3 ± 1.6	$\Delta = -0.13$; 95% CI <0.28 $t = -2.4$; $p = 0.01$
Flu-related non-specific symptoms	2.7 ± 2.2	2.4 ± 2.1	$\Delta = 0.29$; 95% CI <0.47 $t = -1.7$; $p = 0.04$
Respiratory symptoms	2.8 ± 2.5	2.6 ± 2.6	$\Delta = 0.15$; 95% CI <0.45 $t = -2.1$; $p = 0.02$
All influenza symptoms	2.7 ± 2.3	2.5 ± 2.2	$\Delta = 0.22$; 95% CI <0.37 $t = -3.0$; $p = 0.001$

Rafalsky V. et. al. *International Journal of Infectious disease*, 2016, 51: 47-55

STRONG SAFETY

Preclinical studies

- Single-dose toxicity
- General toxicity
- Potential mutagenic properties
- Allergenic properties
- Reproductive toxicity
- Effect on postnatal development
- Immunotoxicity

Results

- No toxic effects have been revealed
- No mutagenic properties have been revealed
- No toxic effects on lactating females (general condition, BW gain) and postnatal development

Clinical safety

- No severe adverse events reported
- Can be safely used in combination with symptomatic and other drugs, on a long term basis / in patients with immunodeficiencies
- Do not cause exhaustion of the immune system

TAKE-HOME MESSAGES

- Modifying activity of the RA drugs
- High safety and absence of adverse effects
- High efficacy in severe respiratory infections management
- Standard drugs' efficacy increase in conjoint use

Released-active drugs represent promising opportunity for being included in standard treatment schemes

Thank you for you attention

The Russian Academy of Sciences
Institute of General Pathology and Pathophysiology
Laboratory of physiologically active substances

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