Cap-dependent Endonuclease Inhibitor S-033188 for the treatment of Influenza: Results from a Phase 3, Randomized, Double-Blind, Placebo- and Active-Controlled Study in Otherwise Healthy Adolescents and Adults with Seasonal Influenza
Capstone-1

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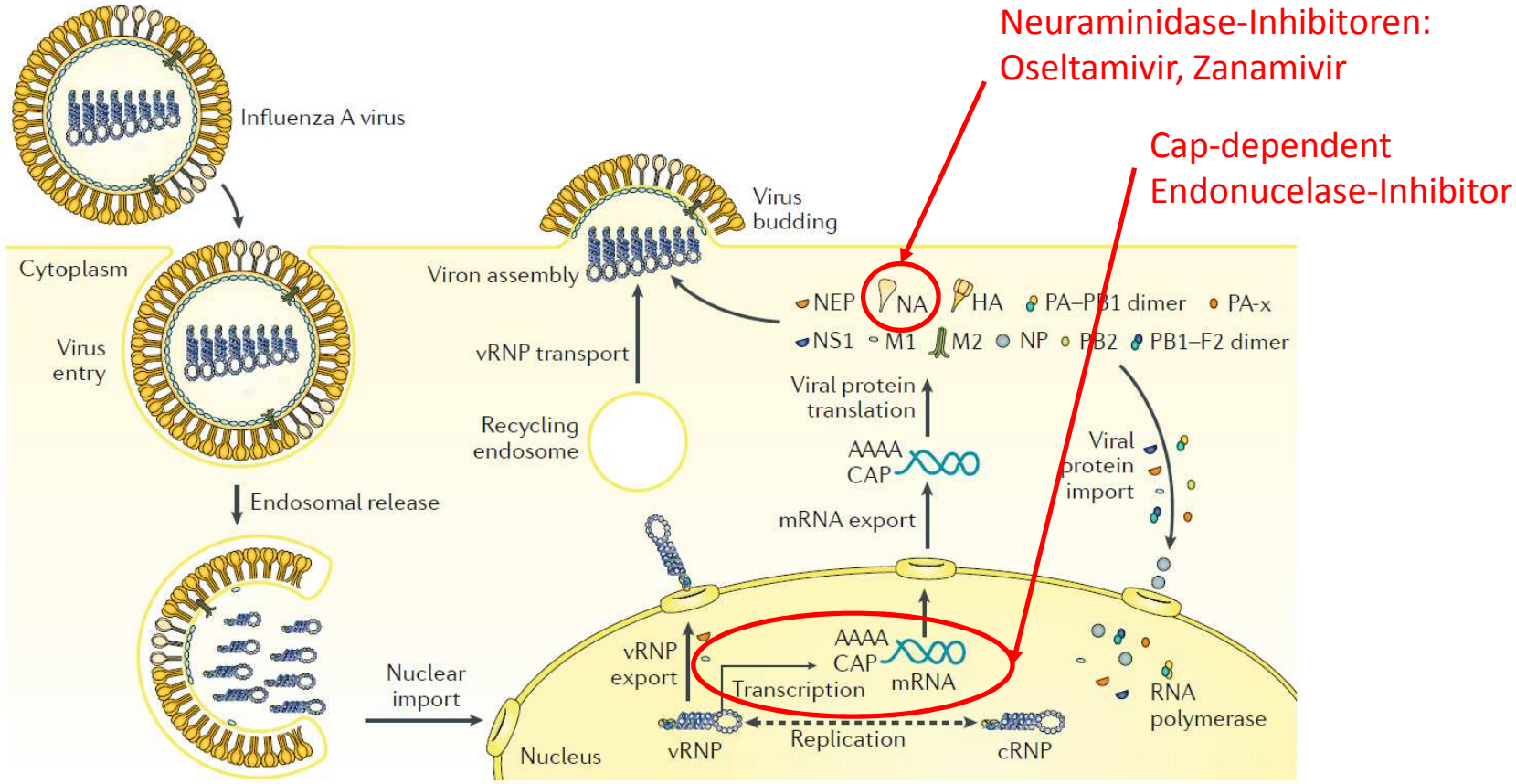
Hintergrund



Krammer et al., Nature Reviews 2018

Hintergrund

Inhibition of Cap (m^7GpppXm)-Dependent Endonuclease of Influenza Virus by 4-Substituted 2,4-Dioxobutanoic Acid Compounds

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A Novel Antiviral Agent Which Inhibits the Endonuclease ... 1994

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Synthesis of Natural Flutimide and Analogous Fully Substituted Pyrazine-2,6-diones, Endonuclease Inhibitors of Influenza Virus

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Methoden

- Multicenter, randomized, double-blind, placebo- and active-controlled study
- Einschlusskriterien: 12-64 Jahre

  + Influenza-like Illness: Fieber (>38°C), min. 1 Allgemeinsymptom, min. 1 respiratorisches Symptom

  Seit <48 Stunden
- Ausschlusskriterien:

  Hospitalisation

  Schwangere, Bewohner von Langzeitpflegeeinrichtungen, chronische Lungenerkrankungen, Herzerkrankungen, endokrine Erkrankungen, Nierenerkrankungen, Lebererkrankungen, metabolische Störungen, Immunsuppression, …..

Methoden

- Randomisierung

  20-64 Jahre: S-033188 40mg oder 80mg einmalig, Oseltamivir 2x75mg/d für 5d oder Placebo

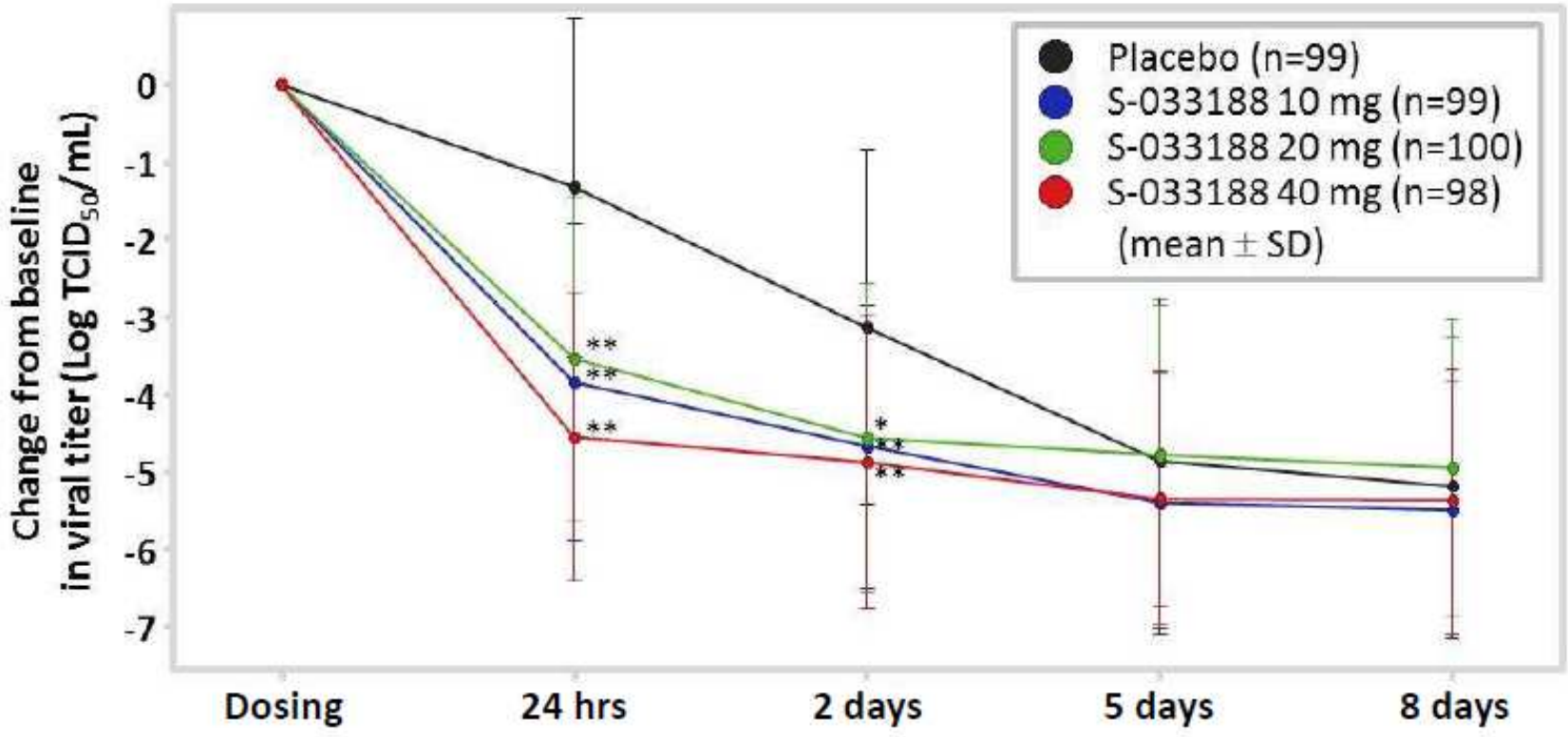
  12-19 Jahre: S-033188 einmalig oder Placebo

- Primäres Outcome: Time to alleviation of symptoms
- Sekundäres Outcome:
  - Nachweisbarer Influenza-Titer
  - Nachweisbare Influenza-Viruslast (PCR)
  - Time to cessation of viral shedding by virus titer or virus RNA (below the limit of quantification)
  - ….

Resultate: 1436 Patienten

	S-033188	**Oseltamivir**	**Placebo**
Time to alleviation of influenza symptoms	53.7 hours	NA	80.2 hours
Median time to cessation of viral shedding	24 hours	72 hours	96 hours
Reduction of viral titer and RNA compared to baseline	«significant greater reduction than Oseltamivir on day 3 or placebo on day 5»		
Adverse events	«generally well tolerated» «lower than Oseltamivir»		

ECCMID 2017: Phase 2 Studie



**p<0.0001, *p<0.001 vs placebo

Watanabe et al., ECCMID 2017

ECCMID 2017: Phase 2 Studie

Adverse events/drug reactions, n (%)	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Adverse events	27 (27.0)	23 (23.0)	26 (26.0)	29 (29.0)
Adverse drug reactions	9 (9.0)	7 (7.0)	6 (6.0)	10 (10.0)

- No deaths, serious adverse events, or adverse events leading to withdrawal were reported in any of the four groups.

Adverse events occurring at an incidence of 3% or higher in either treatment group

Adverse events, n (%)	S-033188 10 mg	S-033188 20 mg	S-033188 40 mg	Placebo
Headache	3 (3.0)	1 (1.0)	4 (4.0)	3 (3.0)
Diarrhoea	0	3 (3.0)	2 (2.0)	5 (5.0)
ALT increased	3 (3.0)	0	2 (2.0)	3 (3.0)
AST increased	3 (3.0)	0	1 (1.0)	1 (1.0)
WBC count decreased	3 (3.0)	1 (1.0)	0	0

Watanabe et al., ECCMID 2017

Konsequenz?

- Zulassung in Japan im Februar 2018 erhalten:
  - Wirkstoffname: Baloxavir marboxil (Xofluza©)
  - Preis: 20mg Tbl. ca. 22 Fr. → 44-88 Fr. pro Behandlung (Tamiflu 86 Fr./10 Tbl.)
- Capstone-2:
  - Gleiches Studiendesign für Patienten mit hohem Risiko für Komplikationen
  - Studie im April 2018 beendet, Resultate noch ausstehend
- FDA-Entscheid für Dezember 2018 erwartet

- In Zukunft kürzere Isolationsdauer möglich?