LIPSOVIR®

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Overall objective – Lipsovir® phase III program

To demonstrate safety and efficacy of Lipsovir

- Prevention of ulcerative herpes episodes (cold sores)
- Reduction in healing time
- Safety profile in adults and adolescents

Summary of results

- Lipsovir is superior to vehicle (placebo) for prevention
- Lipsovir is superior to aciclovir in our cream base (vehicle) for prevention
- Cold sores heal faster with Lipsovir
- Lipsovir is well tolerated in all populations, including immunocompromised patients and adolescents

Lipsovir® phase III program

- Pivotal study in adults with recurrent herpes labialis
  - SAFETY and EFFICACY
- Study in adolescents (12-17 years) with recurrent herpes labialis
  - SAFETY
- Study in immunocompromised patients with recurrent herpes labialis
  - SAFETY
- 2 photosafety studies

Pivotal study

Treatment groups

- Lipsovir
- Aciclovir in our vehicle
- Vehicle (placebo)

- 5-times daily for 5 days
- Patients with recurrent herpes labialis

Definitions

- **Ulcerative recurrence:** A herpes recurrence that leads to a lesion with ulcer, i.e. a cold sore.

- **Non-ulcerative recurrences:** A herpes recurrence that may be visible as redness and/or swelling but does NOT lead to a cold sore.

Endpoints

- **Primary = prevention**
  - Proportion of patients with non-ulcerative recurrences

- **Secondary = episode duration**
  - Time from treatment start until healing of ulcerative and non-ulcerative recurrences

Hypotheses to be tested

1. **Lipsovir > topical aciclovir on prevention, p<0.001**

2. **Lipsovir > vehicle on prevention, p<0.05**

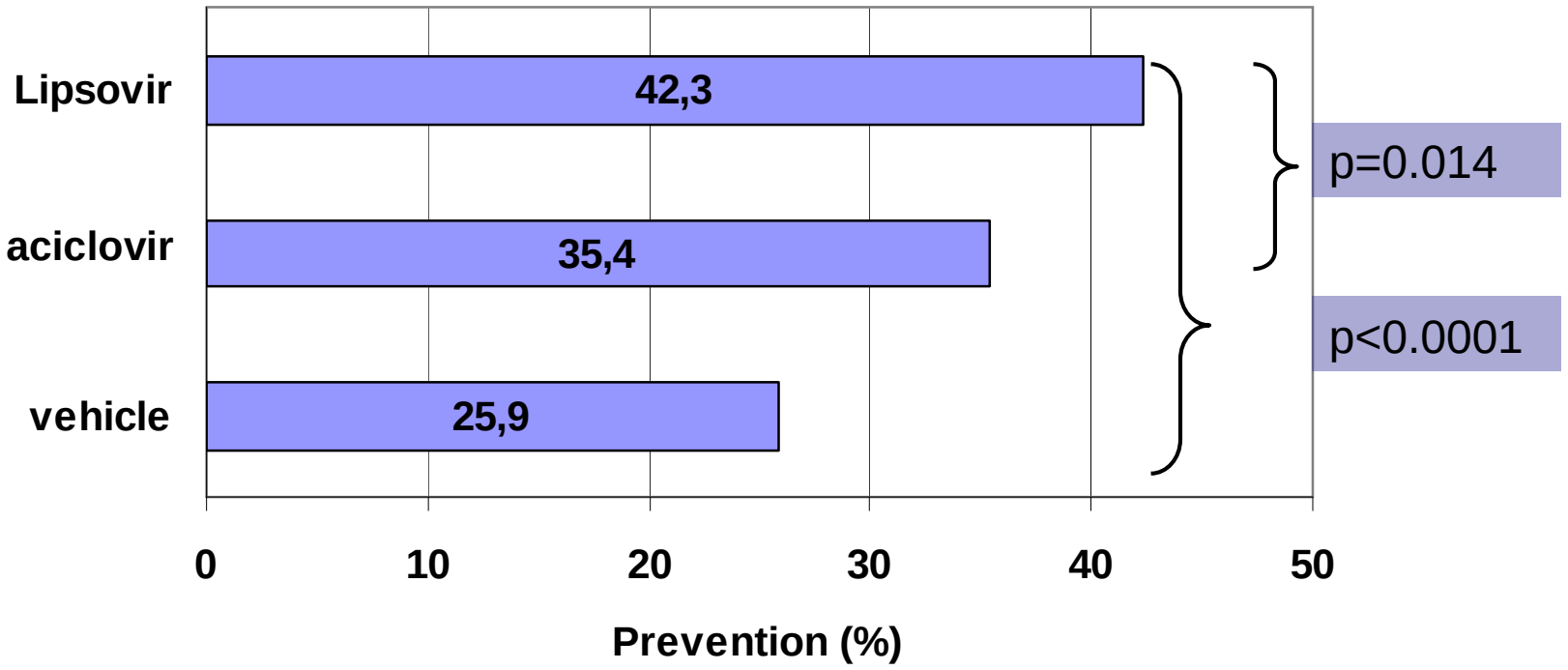
3. **Lipsovir > vehicle on episode duration, p<0.05**

Study sites and study population

Study Centres	64 sites	60 in USA
		4 in Canada

Study Population	2437 randomized
	1443 took at least one dose (ITT-population)

The unique effect



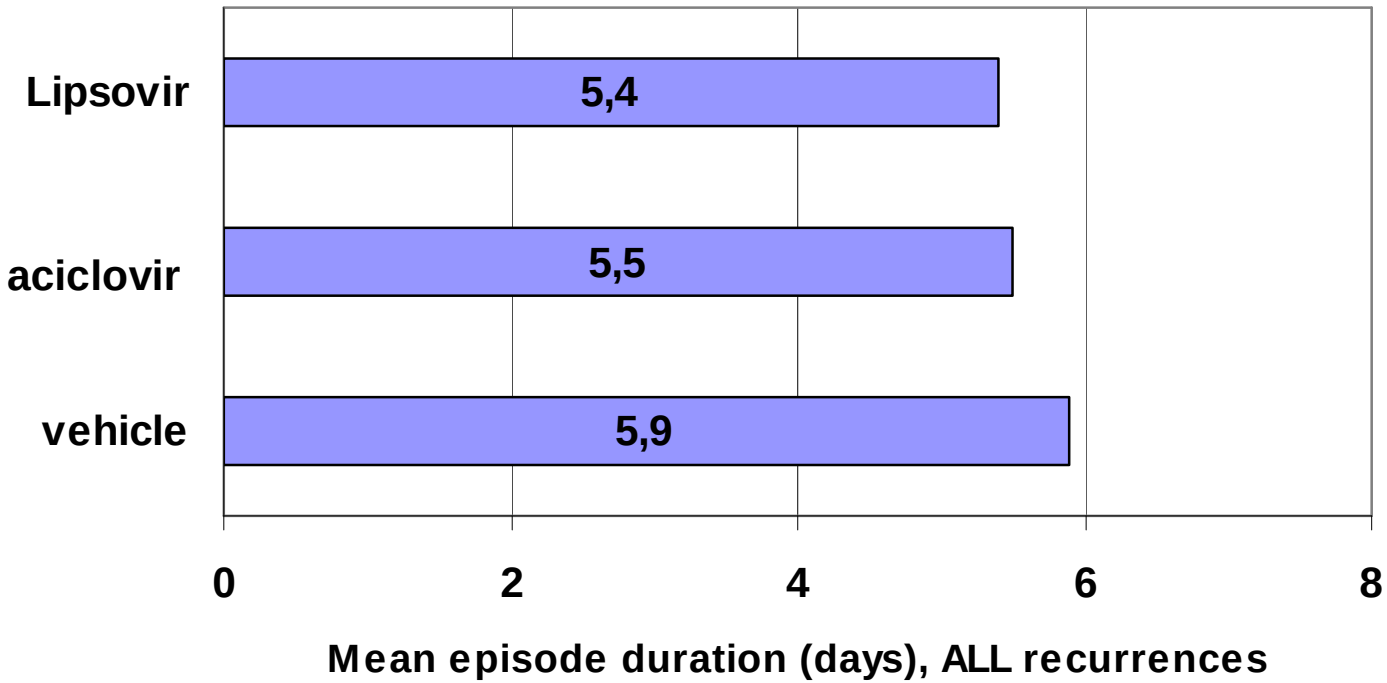
A clinically relevant improvement for patients with cold sores

	Lipsovir	aciclovir	vehicle	Relative improvement vs. aciclovir	Relative improvement vs. vehicle
ITT	42.3 %	35.4%	25.9%	19%	63%

Study patients started treatment early and were compliant

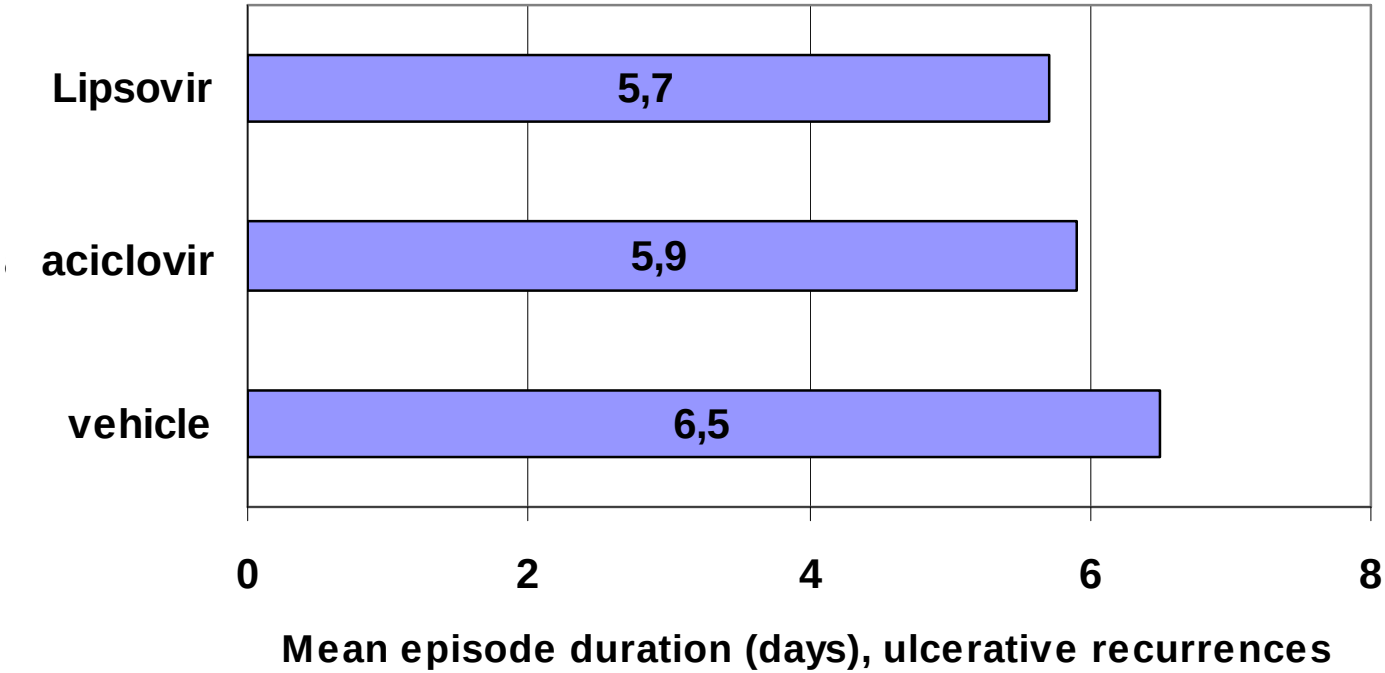
- **92%** started treatment **early** i.e in prodrome or erythema stage
- **0.4 hours** between start of symptoms and start of treatment
- **95%** of the patients were **compliant**

Episode duration (ulcerative + non-ulcerative)



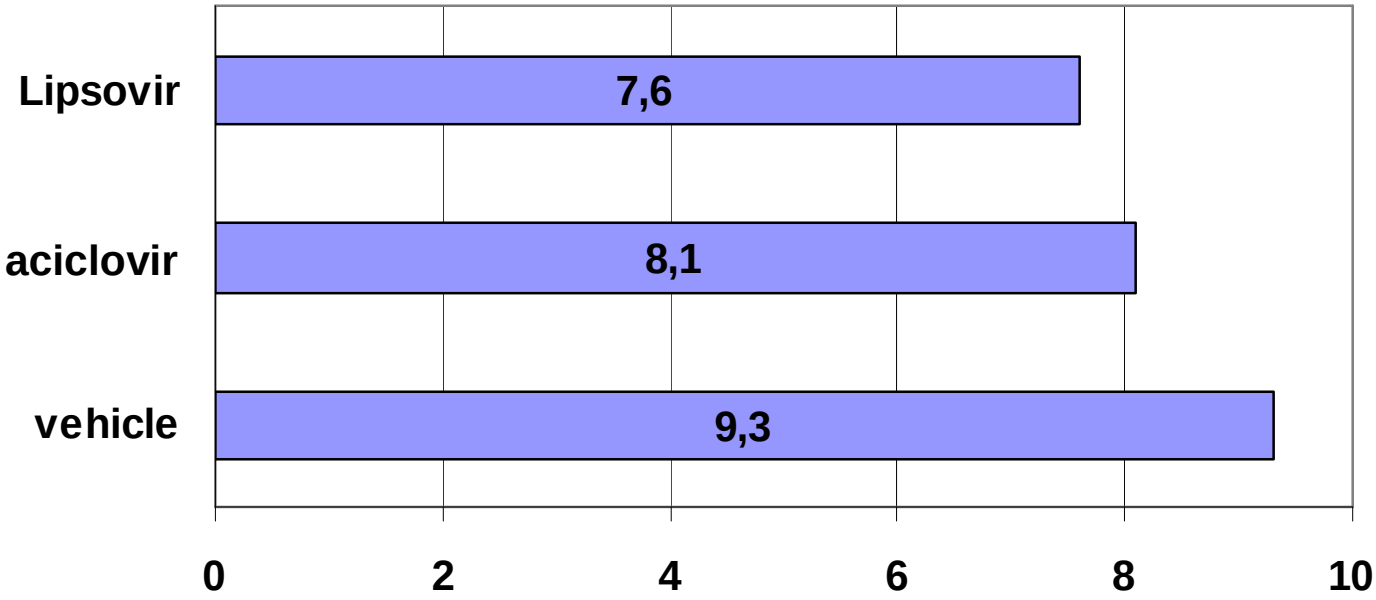
Episode Duration (days) ALL RECURRENCES	Lipsovir (n=601)	aciclovir (n=610)	vehicle (n=232)
Mean (SD)	5.4 (3.00)	5.5 (2.71)	5.9 (3.34)
Difference, p-value		-0.1, p=0.630	-0.5, p=0.057

Cold sores heal faster with Lipsovir®
”loss of hard crust”



Episode Duration (days) ULCERATIVE RECURRENCES	Lipsovir (n=347)	aciclovir (n=394)	vehicle (n=172)
Mean (SD)	5.7 (2.85)	5.9 (2.63)	6.5 (3.27)
Difference, p-value		-0.2, p=0.37	-0.8, p=0.011

Time to normal skin is 1.6 days shorter for Lipsovir®



Mean episode duration to normal skin (days), ALL recurrences

Episode Duration to NS (days) ALL RECURRENCES	Lipsovir (n=601)	aciclovir (n=610)	vehicle (n=232)
Mean (SD)	7.6 (4.17)	8.1 (4.54)	9.3 (5.9)
Difference, p-value		-0.4, p=0.090	-1.6, p<0.0001

Lipsovir® was well tolerated

	Lipsovir (n=601)	aciclovir (n=610)	vehicle (n=232)
TOTAL No. of patients with at least one Adverse Event	18%	16%	19%
Secondary recurrences	9%	10%	12%
Administration site conditions	5%	4%	7%

3 Serious Adverse Events without relationship to study medication

Study in adolescents

Objective

To evaluate the safety of Lipsovir for the treatment of herpes labialis recurrences in immunocompetent adolescents, 12 – 17 years of age.

- **Adverse Events**
- **Categorization of recurrence**
  - Ulcerative/non-ulcerative based on recurrence stage classification
- **Maximum lesion area**

Study was performed in Russia and Sweden

Study Centres	26 sites	20 in Russia
		6 in Sweden

Study Population	254 randomized	
	134 treated with Lipsovir	= safety analysis set

- ✓ **60% of recurrences were non-ulcerative**
- ✓ **Mean maximum lesion size was 39 mm^2 = pivotal study result**

Lipsovir® was well tolerated

- Study treatment was well tolerated
  - limited number of Adverse Events
- One case of application site inflammation in Lipsovir group
  - The cause may have been hypersensitivity or irritation to either aciclovir or hydrocortisone, or to any of the individual ingredients of the vehicle.

Study in immunocompromised patients

Study objective

- To evaluate the **episode duration** of a herpes labialis recurrence when treated with topical administration of **Lipsovir or aciclovir** in immunocompromised adults

- The sample size was determined to **exclude a doubling** of episode duration in either treatment arm

How many patients were treated?

Study Centres	25 sites	19 in Russia
		6 in Ukraine

Study Population	201 randomized
	107 (100%) ITT

Episode duration was similar between Lipsovir® and aciclovir

Episode Duration (days) ITT population	Lipsovir (n=77)	aciclovir (n=30)
Mean* (SD)	6.7 (2.3)	6.7 (2.5)
Primary Analysis		
Median Ratio (Lipsovir/aciclovir) with 95% CI	**0.97 (0.79,1.25)**	

Virology

- Viral swabs were obtained during the ulcer/soft crust stage only (to avoid disturbing the healing process)

- Analysis performed:
  - Quantitative PCR
  - Virus isolation (culturing)
  - Plaque reduction assay (PRA) for aciclovir susceptibility testing
  - Thymidine Kinase (TK) and DNA polymerase sequencing checking for mutations inducing aciclovir resistance

- **NO aciclovir resistant sample was identified in either treatment group**

Lipsovir® was well tolerated

- Treatment Emergent Adverse Events were reported for
  - 6 Lipsovir patients
  - 5 aciclovir patients
- All AEs were of mild or moderate intensity
- One event was considered as related to study drug according to the investigator: application site hypersensitivity
- One Serious Adverse Event (pneumonia) was reported for 1 aciclovir patient.

Primary endpoints and regulatory implications

1. Lipsovir > vehicle on prevention, p<0.05

✓ **Exceeded, p<0.0001**

2. Lipsovir > topical aciclovir on prevention, p<0.001

✓ **Not fully met (p=0.014) based on aciclovir in our vehicle being superior to historical aciclovir cream data**

3. Lipsovir > vehicle on episode duration, p<0.05

✓ **Not fully met (p=0.057) for the combined endpoint (ulcerative + non-ulcerative). Lipsovir showed a pronounced effect on ulcerative episodes. Lipsovir shifted ulcerative episodes to slightly longer non-ulcerative.**

Interpretation

- Lipsovir prevents cold sores

  This is due to the **combined action** of:

  1. aciclovir
  2. hydrocortisone
  3. our cream base (vehicle)

Way forward

- Lipsovir provides an important medical benefit to patients with recurrent labial herpes
- There is no product on the market with a demonstrated preventive effect
- Discussions with regulatory authorities will follow
- The dialogue with potential partners will continue