M.-L. Lauterjung
Klinik für Hepatologie

INSELSPITAL
UNIVERSITÄTSSPITAL BERN
HOPITAL UNIVERSITAIRE DE BERNE
BERN UNIVERSITY HOSPITAL

Ledipasvir and Sofosbuvir for 8 or 12 Weeks for Chronic HCV without Cirrhosis

Massachusetts Medical Society, April 2014
sponsored by Gilead Sciences

Zweck der Studie

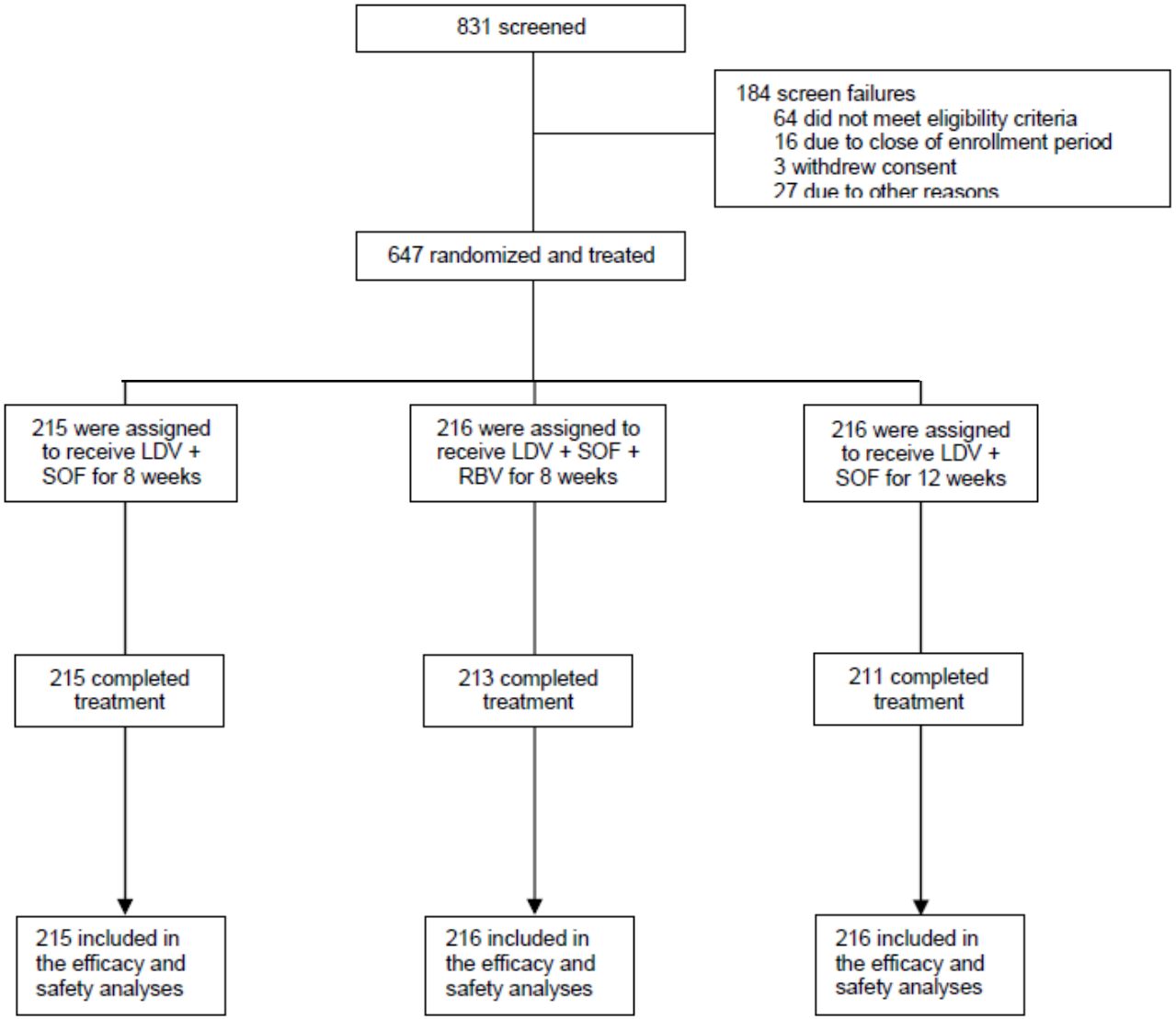
- **Evaluation of safety, tolerability and noninferiority of ledipasvir/ sofosbuvir fixed-dose combination administered 8 or 12 weeks of treatment**
- **Evaluation of the additional benefit of including ribavirin into the fix combination (in 8 weeks treatment)**

Studiendesign

- **phase 3**
- **multicenter, randomized, open-label**

Patienten

- **647 patients with chronich HCV genotype 1 infection**
  - no cirrhosis
  - treatment-naive
  - 18 y and older, HCV RNA > 10,000 IU/ml, ALAT/ASAT < 10x normal range, platelet count > 90.000/mm^2, Hb > 11 g/dl ♂ or 12 g/dl ♀
- **enrolled between May 2013 and June 2013**
- **randomization into (1:1:1)**
  - ledipasvir-sofosbuvir for 8 weeks (215 patients)
  - ledipasvir-sofosbuvir-ribavirin for 8 weeks (216 patients)
  - ledipasvir-sofosbuvir for 12 weeks (216 patients)


831 screened
184 screen failures
64 did not meet eligibility criteria
16 due to close of enrollment period
3 withdrew consent
27 due to other reasons
647 randomized and treated
215 were assigned to receive LDV + SOF for 8 weeks
216 were assigned to receive LDV + SOF + RBV for 8 weeks
216 were assigned to receive LDV + SOF for 12 weeks
215 completed treatment
213 completed treatment
211 completed treatment
215 included in the efficacy and safety analyses
216 included in the efficacy and safety analyses
216 included in the efficacy and safety analyses

Assessment

- **Primary End Point**
  - **Sustained Virologic Response: HCV RNA < 25 IU/ml**
    12 weeks after end of therapy

- **Screening and Assessment during treatment**
  - **viral load: serum HCV RNA level**
  - **HCV and IL28B genotyping**
  - **standard laboratory, physical examination, electrocardiography**
  - **liver biopsy (METAVIR Score)**
  - **deep sequencing of NS5A and NS5B regions of HCV RNA**

Ergebnisse

Rates of SVR 12 weeks after end of therapy

- **ledipasvir-sofosbuvir 8 wk treatment: 94% (95% CI 90-97)**
- **ledipasvir-sofosbuvir-ribavirin 8 wk treatment: 93% (95% CI 89-96)**
- **ledipasvir-sofosbuvir 12 wk treatment: 95% (95% CI 92-98)**

Virologic failure

- **no nonresponse or virologic breakthrough during treatment in any group**
- **overall: relapse in 23 patients**
- **ledipasvir-sofosbuvir 8 wk: 11 (5%)**
- **ledipasvir-sofosbuvir-ribavirin 8 wk: 9 (4%)**
- **ledipasvir-sofosbuvir 12 wk: 3 (1%)**

Table 2. Response during and after Treatment.

Response	LDV–SOF for 8 Wk (N=215)	LDV–SOF + RBV for 8 Wk (N=216)	LDV–SOF for 12 Wk (N=216)
HCV RNA <25 IU/ml			
During treatment period — no./total no. (%)*			
At wk 2	190/215 (88)	195/214 (91)	197/216 (91)
At wk 4	215/215 (100)	211/213 (99)	216/216 (100)
After end of treatment — no. (%)			
At wk 4	207 (96)	205 (95)	208 (96)
At wk 12	202 (94)	201 (93)	206 (95)
Virologic failure during treatment — no.	0	0	0
Relapse in patients with HCV RNA <25 IU/ml at end of treatment — no. (%)	11 (5)	9 (4)	3 (1)
Lost to follow-up — no.	1	5	7
Withdrew consent — no.	1	1	0

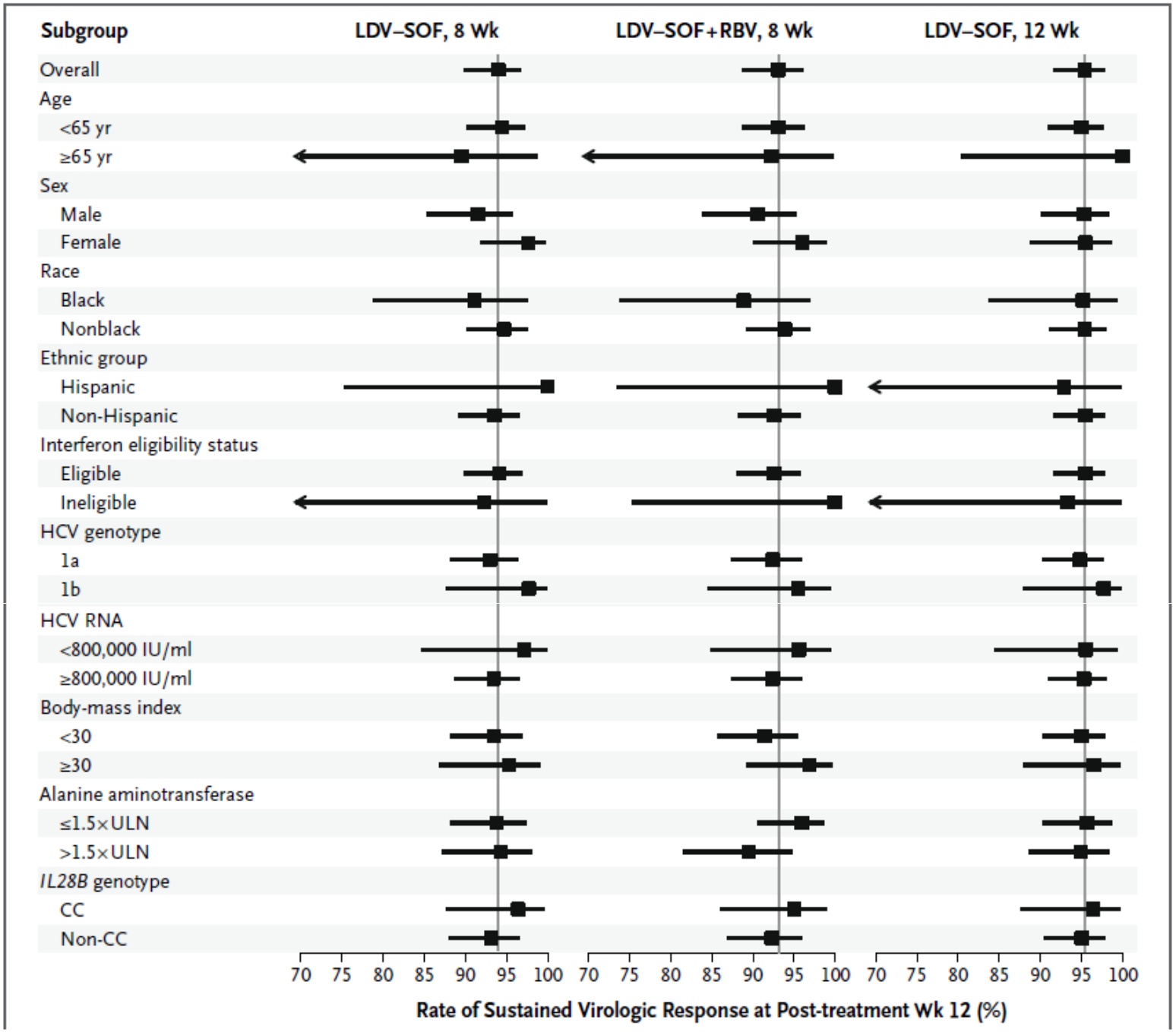

Subgroup
LDV–SOF, 8 Wk
LDV–SOF+RBV, 8 Wk
LDV–SOF, 12 Wk
Overall
Age
<65 yr
≥65 yr
Sex
Male
Female
Race
Black
Nonblack
Ethnic group
Hispanic
Non-Hispanic
Interferon eligibility status
Eligible
Ineligible
HCV genotype
1a
1b
HCV RNA
<800,000 IU/ml
≥800,000 IU/ml
Body-mass index
<30
≥30
Alanine aminotransferase
≤1.5×ULN
>1.5×ULN
IL28B genotype
CC
Non-CC
70 75 80 85 90 95 100
Rate of Sustained Virologic Response at Post-treatment Wk 12 (%)

Table S7. SVR12 by Metavir Stage in Subjects Whose Fibrosis was Determined by Liver Biopsy

	ION-3		
	LDV/SOF 8 Weeks (N=215)	LDV/SOF+RBV 8 Weeks (N=216)	LDV/SOF 12 Weeks (N=216)
Metavir Score			
F0	20/22 (90.9%)	12/13 (92.3%)	16/16 (100.0%)
95% CI	70.8% to 98.9%	64.0% to 99.8%	79.4% to 100.0%
F1	60/62 (96.8%)	43/46 (93.5%)	55/59 (93.2%)
95% CI	88.8% to 99.6%	82.1% to 98.6%	83.5% to 98.1%
F2	40/43 (93.0%)	47/49 (95.9%)	51/52 (98.1%)
95% CI	80.9% to 98.5%	86.0% to 99.5%	89.7% to 100.0%
F3	28/29 (96.6%)	24/28 (85.7%)	28/29 (96.6%)
95% CI	82.2% to 99.9%	67.3% to 96.0%	82.2% to 99.9%
F4	0/0	0/0	0/0
95% CI			

Ergebnisse

- **Virologic Resistance Testing**
  - **In 116 patients resistance associated variants were detected**
  - **of these 116 patients 104 had SVR (90%)**
  - **of the 23 patients with relaps 15 had resistance associated variants at the time of relaps**
  - **of these 15, 9 had virants at baseline and 6 did not**

Ergebnisse: Adverse events

- **3 patients discontinued treatment: 1 due to a road accident, 1 to arthralgia, 1 to lung cancer**
- **no patient discontinued therapy in LDV-SOF 8 wk-regime**
- **10 patients showed serious adverse events, no single event occurred in more than 1 patient**

- **Rates**
  - **ledipasvir-sofosbuvir 8 wk: 67%**
  - **ledipasvir-sofosbuvir-ribavirin 8 wk: 76%**
  - **ledipasvir-sofosbuvir 12 wk: 69%**

- **Change in Haemoglobin Level**
  - **ledipasvir-sofosbuvir 8 wk: - 0,2 g/dl**
  - **leidpasvir-sofosbuvir-ribavirin 8 wk: - 1,9 g/dl**
  - **ledipasvir-sofosbuvir 12 wk: - 0,4 g/dl**

Table 3. Treatment Discontinuations, Adverse Events, and Hematologic Abnormalities.*

Variable	LDV–SOF for 8 Wk (N=215)	LDV–SOF + RBV for 8 Wk (N=216)	LDV–SOF for 12 Wk (N=216)
Duration of treatment — wk	8.1±0.2	8.0±0.9	12.0±0.9
Discontinuation of ledipavir–sofosbuvir owing to adverse event — no. of patients (%)	0	1 (<1)	2 (1)
Serious adverse event — no. of patients (%)	4 (2)	1 (<1)	5 (2)
Any adverse event — no. of patients (%)	145 (67)	165 (76)	149 (69)
Common adverse event — no. of patients (%)†			
Fatigue	45 (21)	75 (35)	49 (23)
Headache	30 (14)	54 (25)	33 (15)
Nausea	15 (7)	38 (18)	24 (11)
Insomnia	11 (5)	26 (12)	15 (7)
Irritability	3 (1)	29 (13)	9 (4)
Diarrhea	15 (7)	13 (6)	9 (4)
Arthralgia	9 (4)	11 (5)	16 (7)
Constipation	9 (4)	13 (6)	8 (4)
Dizziness	6 (3)	13 (6)	9 (4)
Rash	3 (1)	19 (9)	5 (2)
Pruritus	2 (1)	16 (7)	5 (2)
Cough	3 (1)	12 (6)	7 (3)
Anemia	2 (1)	17 (8)	2 (1)
Muscle spasms	3 (1)	11 (5)	6 (3)
Dyspnea	0	11 (5)	1 (<1)
Hematologic abnormality — no. of patients (%)			
Hemoglobin level <10 g/dl	0	11 (5)	1 (<1)
Lymphocyte count 350 to <500 per mm^3	0	1 (<1)	0
Neutrophil count 500 to <750 per mm^3	0	1 (<1)	1 (<1)

Bewertung

- **in all three groups the SVR rates were higher than the historical control rate of 60%, in fact higher than 90%**
- **8 wk therapy with ledipasvir-sofosbuvir is noninferior to 12 wk**
- **the rate of adverse events was higher in combination with ribavirin**
- **adding ribavirin didn‘t increase efficacy**
- **response rates didn‘t vary substantially according to patients demographic or clinical characteristics at baseline**
  -> good rates also in patients known to have poor response
- **relapse rate in LDV-SOF for 8 wk was higher than in 12 wk regime, but generally low and without sufficient characteristics**

Bewertung

- **in a different small study 25 patients were treated with ledipasvir-sofosbuvir for 6 weeks**
- **17 (68%) showed sustained virologic response, 8 had relapse**

Fazit

So this study could show…

- **8-week might be the shortest effective duration for ledipasvir-sofosbuvir fixed-dose treatment regime**
- **the regime may be appropriate for a broad range of previously untreated patients**
- **eliminating ribavirin decreases the rate of side effects with no loss in efficacy**

Vielen Dank für Ihre Aufmerksamkeit!