Telaprevir in combination with peginterferon and ribavirin in ex-people who inject drugs with chronic hepatitis C: interim results of the INTEGRATE study

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Background

- In 2010, ~10 million people who inject drugs (PWID) were HCV antibody positive globally[1]
- The Global and EU prevalence of HCV in PWID is ranging between 40% and 67%[1–3]
- Injection drug use is the primary source of new HCV infections in developed countries[2,4]
- In chronic HCV studies of pegylated-interferon + ribavirin (PR), the sustained virologic response (SVR) rate among PWIDs (irrespective of prior or current injecting drug use) appears to be comparable to rates among non-PWIDs[5,6]
  - SVR rate with first-generation DAAs in patients with HCV G1 monoinfection is 70–80%[6,7]
  - However this has not been confirmed in the PWID population
- The greatest barriers to treatment for this group of patients are:
  - Lack of knowledge/facilities in addiction clinics
  - Concern regarding treatment adherence

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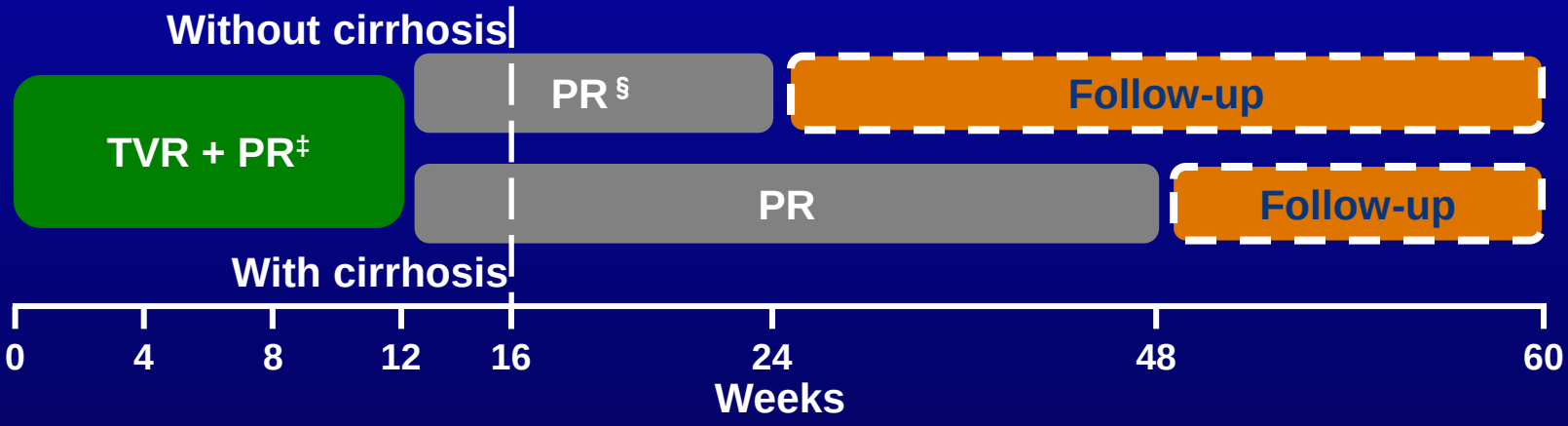
INTEGRATE: study design

- A multicentre, observational, prospective study conducted in Belgium, France, Germany, Switzerland, The Netherlands and UK (NCT01980290)
- The study enrolled ex-PWID with genotype 1 chronic HCV infection, naïve and relapsers, under substitution therapy and/or followed in addiction centres
- Patients enrolled should be treated within the telaprevir and Peg-IFN/ribavirin (TVR/PR)*



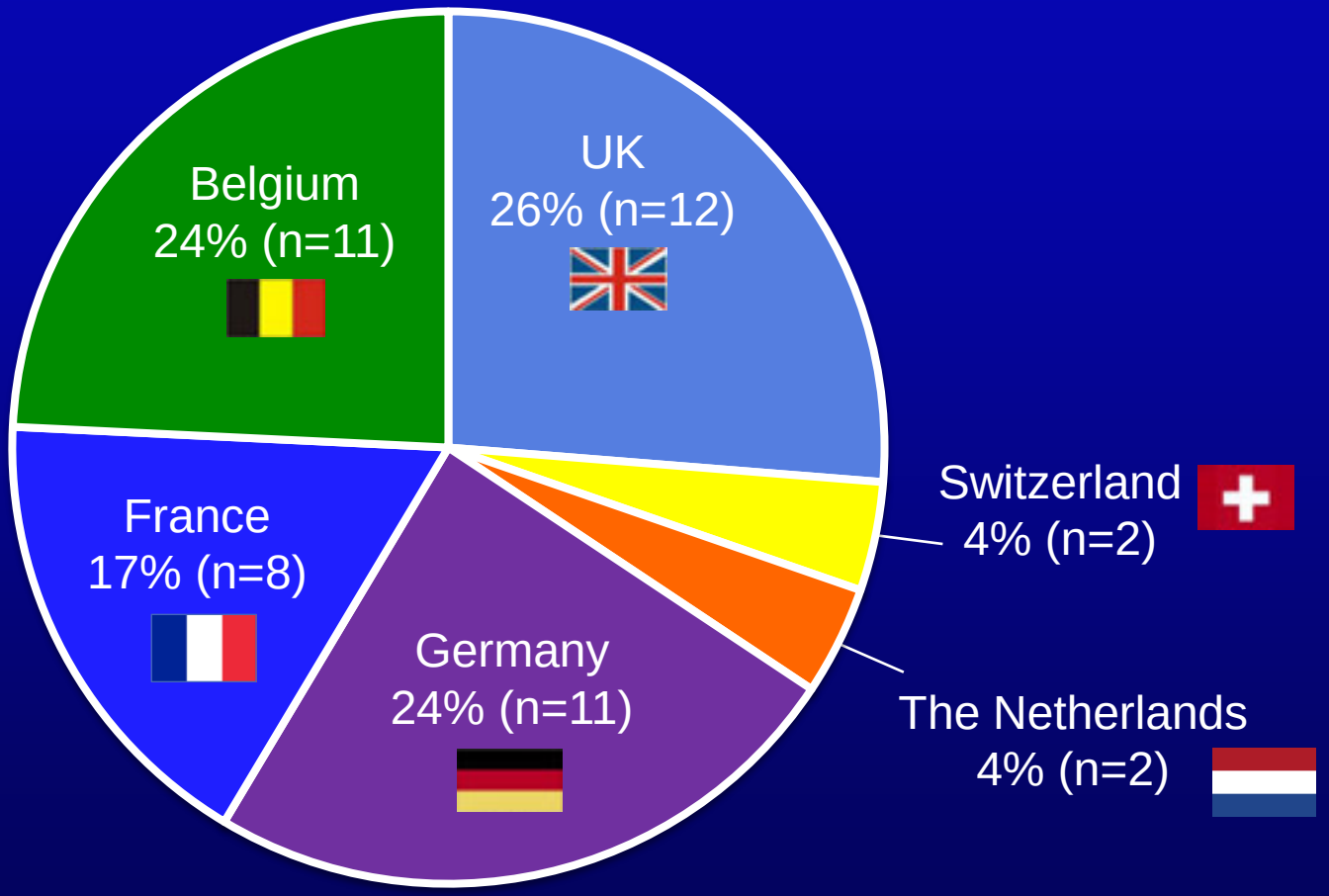
Here we present the results of an interim analysis conducted on data up to Week 16

*No PR lead-in and standard stopping rules were applied
TVR, PegIFN alfa/ and RBV were prescribed by the participating health care provider in accordance with approved local labels
§ Stop treatment at Week 24 if HCV RNA undetectable at Weeks 4 and 12; continue PR to Week 48 if HCV RNA detectable

Study objectives

- Primary objective:
  - Evaluate the efficacy of telaprevir (TVR), based on sustained virological response (SVR) as measured by HCV RNA <25 IU/mL, at 12 weeks (SVR12) after the last dose of treatment
- Secondary objectives:
  - Tolerability and safety of TVR, in combination with PR
  - Adherence to TVR and PR as measured by pill count
  - Assessment of patient-reported outcomes
    - Modified Medication Adherence Self-Report Inventory Questionnaire (M-MASRI)
    - Health-related quality of life based (EQ-5D)
    - Hospital Anxiety and Depression Scale (HADS)
    - Alcohol Use Disorders Identification Test (AUDIT)

Enrollment by Country (ITT, N=46)



The totals do not add up to 100% due to rounding

Patient disposition

	Treatment naïve n (%)	Relapsers n (%)	Total n (%)
Screened	47 (100)	5 (100)	52 (100)
Treated	44 (94)	5 (100)	49 (94)
Intent-to-treat*	42 (89)	4 (80)	46 (88)
Completed	4 (10)	0	4 (9)
Discontinued	11 (26)	1 (25)	12 (26)
Adverse event	4 (10)	0	4 (9)
Lost to follow up	5 (12)	0	5 (11)
Protocol violation	0	1 (25)	1 (2)
Other‡	2 (5)	0	2 (4)
Ongoing	27 (64)	3 (75)	30 (65)

*Intent-to-treat: enrolled, dosed with TVR and had a post-baseline visit
‡One patient unable to read English, one patient had breakthrough

Patient baseline demographic and disease characteristics

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
Age (years), median (range)	43 (28–57)	46 (30–56)	44 (28–57)
Age ≤45 years, n (%)	26 (62)	2 (50)	28 (61)
White, n (%)	38 (90)	4 (100)	42 (91)
Male, n (%)	37 (88)	3 (75)	40 (87)
Body mass index (kg/m²)	N=39	N=3	N=42
Median (range)	25 (17–36)	26 (22–27)	25 (17–36)
HCV subtype, n (%)			
1a	34 (81)	3 (75)	37 (80)
1b	6 (14)	1 (25)	7 (15)
Other (unspecified)	2 (5)	0	2 (4)
Fibrosis stage, n (%)*			
F0–1	14 (33)	2 (50)	16 (35)
F2	7 (17)	0	7 (15)
F3	4 (10)	1 (25)	5 (11)
F4	7 (17)	0	7 (15)
Baseline VL ≥800,000 IU/mL, n (%)	26 (62)	2 (50)	28 (61)

*11 patients had indeterminate fibrosis stage but were confirmed to be non-cirrhotic
VL = viral load

Drug use history

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
Age at first drug use (years)	N=27	N=2	N=29
Median (range)	20 (12–40)	17 (16–18)	19 (12–40)
Previous heroin user, n (%)	31 (74)	2 (50)	33 (72)
Frequency of heroin use, n (%)	N=31	N=2	N=33
Daily	10 (32)	1 (50)	11 (33)
Weekly	7 (23)	0	7 (21)
Last time heroin used, n (%)	N=31	N=2	N=33
Within the last month	5 (16)	0	5 (15)
1–6 months ago	2 (6)	1 (50)	3 (9)
>6 months ago	24 (77)	1 (50)	25 (76)
Previous cocaine user, n (%)	13 (31)	1 (25)	14 (30)
Frequency of cocaine use, n (%)	N=13	N=1	N=14
Daily	3 (23)	0	3 (21)
Weekly	4 (31)	0	4 (29)
Other	3 (23)	0	3 (21)
Last time cocaine used, n (%)	N=13	N=1	N=14
Within the last month	3 (23)	0	3 (21)
>6 months ago	10 (77)	1 (100)	11 (79)

Relevant psychiatric medical history

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
At least one psychiatric disorder (n, %)	18 (43)	1 (25)	19 (41)
Depression	11 (26)	1 (25)	12 (26)
Anxiety	6 (14)	0	6 (13)
Insomnia	2 (5)	0	2 (4)
Schizophrenia	2 (5)	0	2 (4)
Affective disorder	1 (2)	0	1 (2)
Paranoia	1 (2)	0	1 (2)
Personality disorder	1 (2)	0	1 (2)
Psychotic disorder	1 (2)	0	1 (2)

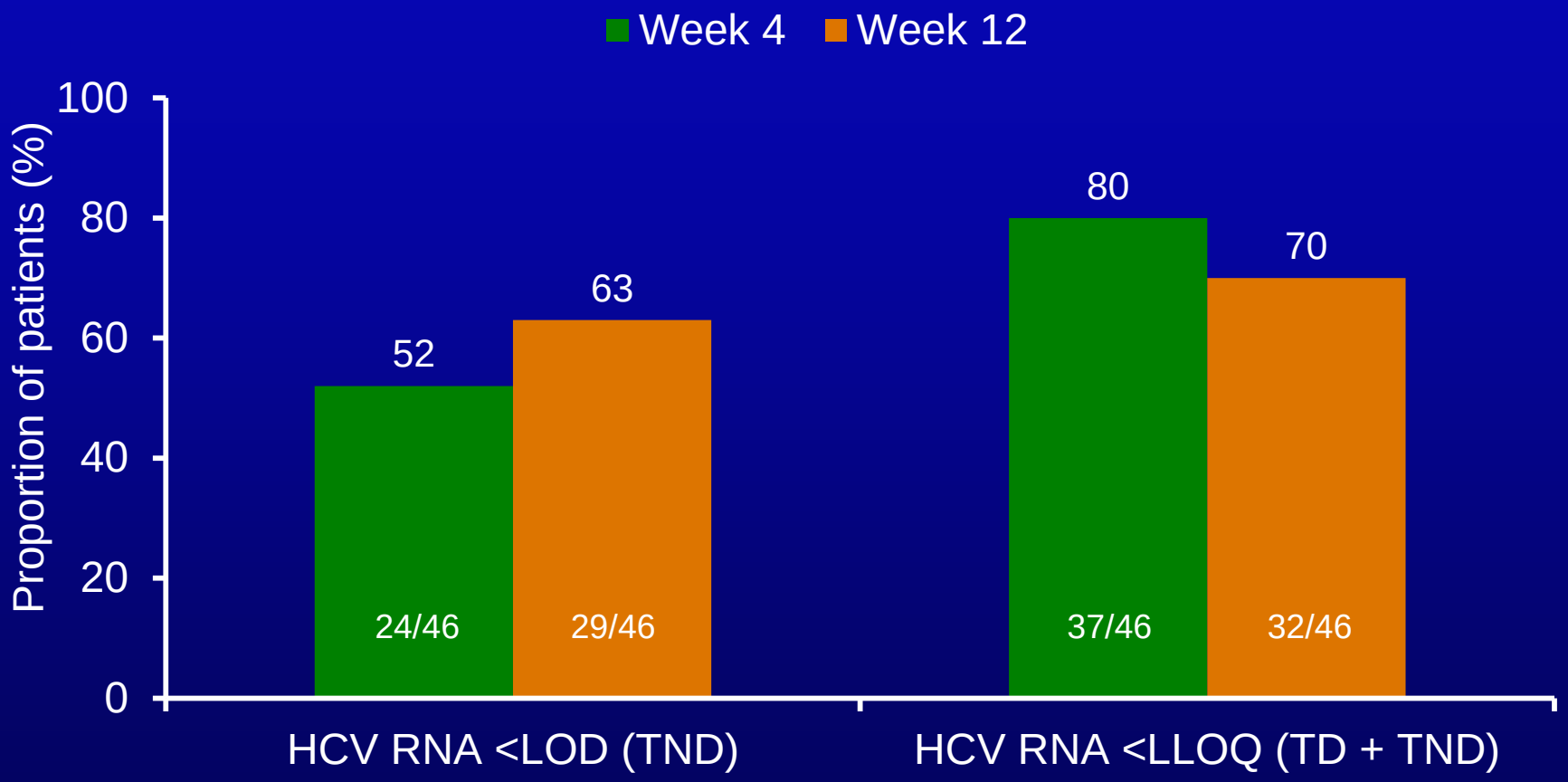
Addiction management at baseline

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
Followed in Addiction Centres, n (%)	41 (98)	4 (100)	45 (98)
On substitution therapy, n (%)	38 (90)	4 (100)	42 (91)
Methadone	30 (71)	2 (50)	32 (70)
Buprenorphine	8 (19)	2 (50)	10 (22)

Anti-anxiety and antidepressant use at baseline

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
Patients with any concomitant medication, n (%)	18 (43)	0	18 (39)
Benzodiazepine derivatives and other anxiolytics	13 (31)	0	13 (28)
Antidepressants	12 (29)	0	12 (26)

Overall on-treatment virologic response (ITT; n=46)



eRVR (HCV RNA <25 IU/mL, TND at Weeks 4 and 12) was 41%

LOD: limit of detection (15 IU/mL); LLOQ: lower limit of quantification (25 IU/mL based on the Roche High Pure System COBAS Taqman® HCV test, other tests may have been used in the study); eRVR: extended rapid virologic response
TD = target detected; TND = target not detected

All AEs reported in >10% of patients

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
Patients with AEs, n (%)	39 (93)	3 (75)	42 (91)
Anemia SSC*	18 (43)	1 (25)	19 (41)
Thrombocytopenia	12 (29)	1 (25)	13 (28)
Fatigue	12 (29)	0	12 (26)
Pruritus	9 (21)	1 (25)	10 (22)
Rash SSC*	9 (21)	0	9 (20)
Leukopenia	7 (17)	1 (25)	8 (17)
Nausea	7 (17)	1 (25)	8 (17)
Headache	7 (17)	0	7 (15)
Vomiting	7 (17)	0	7 (15)
Decreased appetite	5 (12)	1 (25)	6 (13)
Influenza-like illness	6 (14)	0	6 (13)
Irritability	6 (14)	0	6 (13)
Depression	4 (10)	1 (25)	5 (11)

AEs: adverse events
*SSC: special search category

Serious adverse events

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
Patients with serious AEs, n (%)	9 (21)	0	9 (20)
Acute psychosis	1 (2)	0	1 (2)
Anemia*	1 (2)	0	1 (2)
Anxiety	1 (2)	0	1 (2)
Conversion disorder	1 (2)	0	1 (2)
Mental disorder	1 (2)	0	1 (2)
Malaise	1 (2)	0	1 (2)
Pancreatitis	1 (2)	0	1 (2)
Acute renal failure	1 (2)	0	1 (2)
Rash‡	1 (2)	0	1 (2)
Thrombosis	1 (2)	0	1 (2)

Of these serious AEs, anemia and acute renal failure were considered to be at least possibly related to TVR

No deaths were reported during the study

*severe
‡mild

AEs of special interest

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
Patients with SSC AEs, n (%)	28 (67)	2 (50)	30 (65)
Anemia SSC*	18 (43)	1 (25)	19 (41)
Anemia	17 (40)	1 (25)	18 (39)
Decreased hemoglobin	1 (2)	0	1 (2)
Pancytopenia	1 (2)	0	1 (2)
Rash SSC‡	9 (21)	0	9 (20)
Rash	5 (12)	0	5 (11)
Eczema	2 (5)	0	2 (4)
Drug eruption	1 (2)	0	1 (2)
Skin lesion	1 (2)	0	1 (2)
Urticaria	1 (2)	0	1 (2)

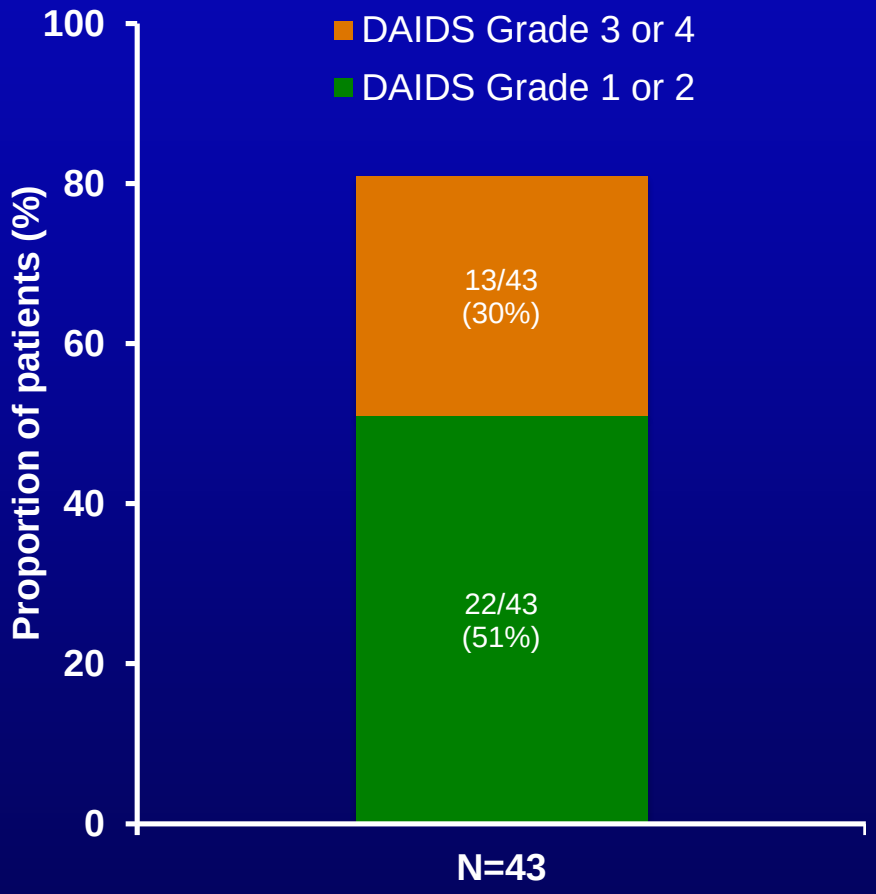
*Grade 1: Hb 10.0–10.9 g/dL or any decrease of 2.5–3.4 g/dL
Grade 2: Hb 9.0–9.9 g/dL or any decrease of 3.5–4.4 g/dL
Grade 3: Hb 7.0–8.9 g/dL or any decrease >4.5 g/dL; Grade 4: Hb <7.0 g/dL
‡Three patients experienced mild rash, two patients moderate rash and no cases of severe rash, SJS or DRESS were reported
SJS: Stevens–Johnson syndrome
DRESS: drug reaction with eosinophilia and systemic symptoms

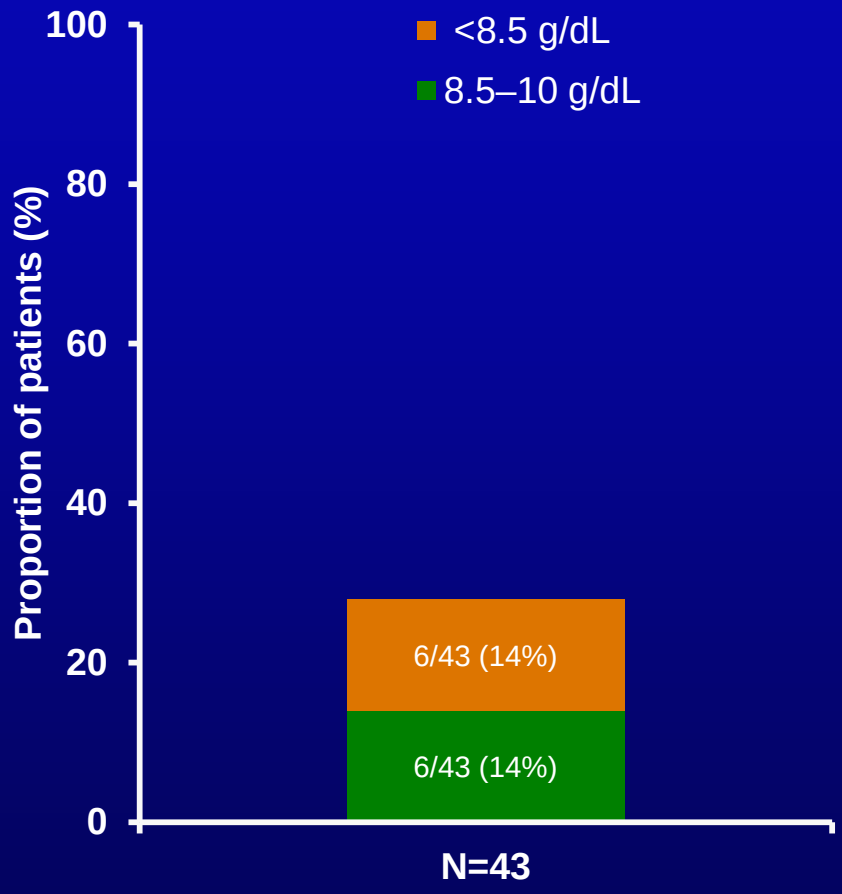
AEs leading to TVR discontinuation

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
Patients with AEs, n (%)*	3 (7)	1 (25)	4 (9)
Acute psychosis (severe)	1 (2)	0	1 (2)
Drug eruption (moderate)	1 (2)	0	1 (2)
Malaise (severe)	0	1 (25)	1 (2)
Thrombocytopenia (severe)	1 (2)	0	1 (2)

*One patient discontinued TVR but not PR

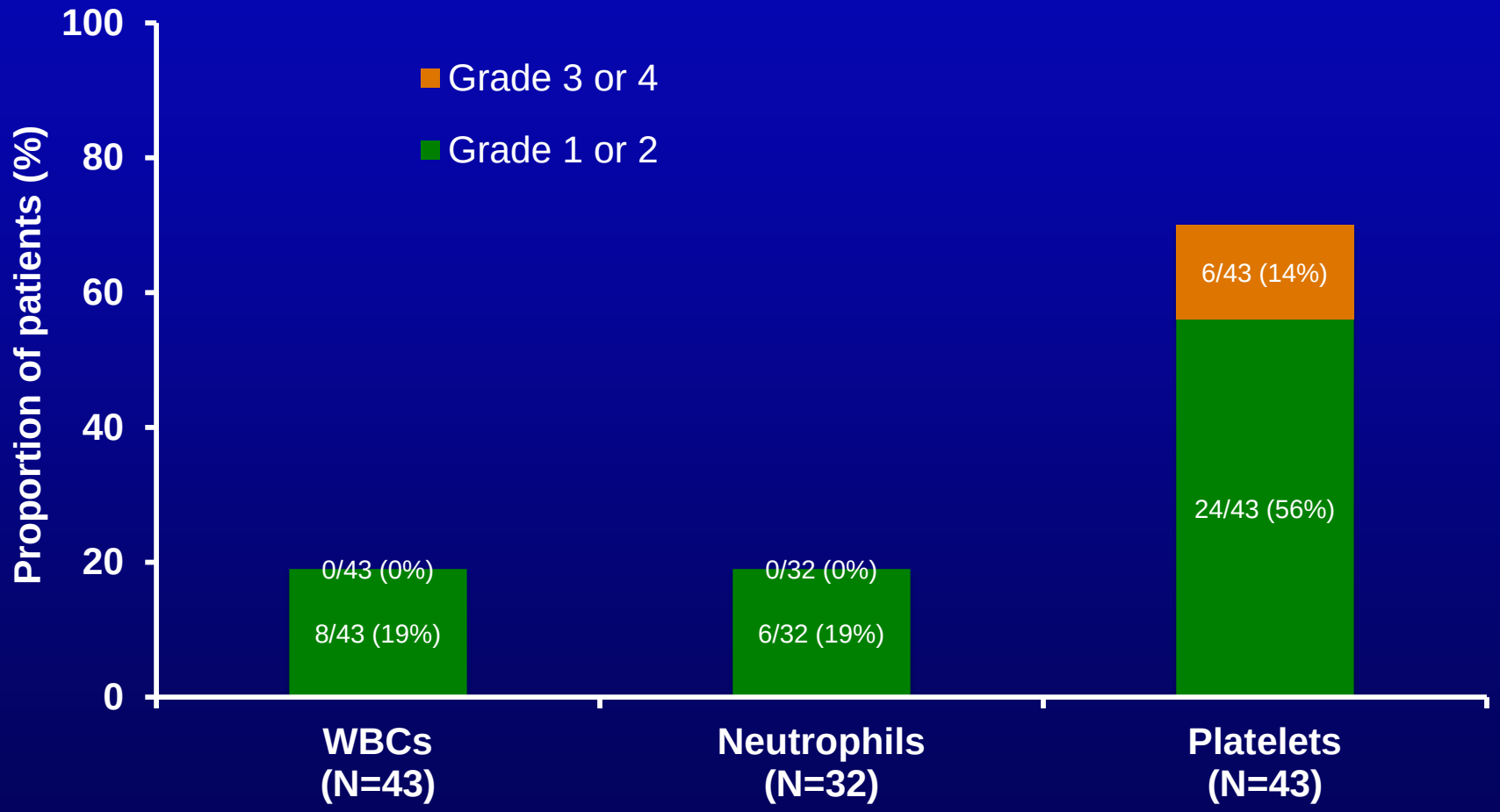
Patients with hemoglobin abnormalities





DAIDS Grade 1 or 2: 9.0–10.9 g/dL or decrease of 2.5–4.4 g/dL
DAIDS Grade 3 or 4: ≤8.9 g/dL or any decrease >4.5 g/dL

Patients with changes in WBCs, neutrophils and platelets



WBCs: white blood cells

Telaprevir treatment adherence at Weeks 4 and 12

	Treatment naïve (N=42)	Relapsers (N=4)	Total (N=46)
Week 4; N	31	2	33
≥90%, n (%)	25 (81)	0	25 (76)
Mean (SD)	97 (6.9)	75 (NA)	95 (8.5)
Week 12; N	20	1	21
≥90%, n (%)	16 (80)	1 (100)	17 (81)
Mean (SD)	94 (13.1)	100 (NA)	94 (12.8)

Conclusions

- In this observational study (week 16 interim analysis) of ex-PWID:
  - 63% of patients had undetectable HCV RNA at Week 12; 41% of patients achieved eRVR, giving the opportunity to non cirrhotic to shorten treatment duration to 24 weeks
  - The safety and tolerability of TVR plus Peg-IFN/RBV was comparable with that previously observed in HCV mono-infected patients with no history of previous drug use
  - Patients reported good adherence to treatment and study procedures

INTEGRATE study investigators

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