Paritaprevir/ritonavir/ombitasvir, dasabuvir with and without ribavirin in people with HCV genotype 1 and recent injecting drug use or receiving OST: The D3FEAT study

Brian Conway[1], Jason Grebely[2], Chris Fraser[3], Alberto Moriggia[4], Evan B Cunningham[2], Ed Gane[5], Catherine Stedman[6], Curtis Cooper[7], Erika Castro[8], Patrick Schmid[9], Kathy Petoumenos[2], Behzad Hajarizadeh[2], Philippa Marks[2], Amanda Erratt[2], Sharmila Siriragavan[2], Olav Dalgard[10], Karine Lacombe[11], Jordan J Feld[12], Julie Bruneau[13], Jean-Pierre Daulouede[14], Jeff Powis[15], Philip Bruggmann[16], Gail V Matthews[2,17], Ian Kronborg[18], David Shaw[19], Adrian Dunlop[20], Tanya L Applegate[2], Sione Crawford[21], and Gregory J Dore[2,11] on behalf of the D3FEAT Study Group

[1]Vancouver Infectious Diseases Center, Vancouver, Canada,[2]The Kirby Institute, UNSW Sydney, Sydney, Australia, [3]Coolaid Community Health Centre, Victoria, Canada, [4]Fondazione Epatocentro Ticino, Lugano, Switzerland, [5]Auckland Hospital, Auckland, New Zealand, [6]Christchurch Hospital and University of Otago, Christchurch, New Zealand, [7]Ottawa Hospital Research Institute, Ottawa, Canada, [8]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [9]Kantonsspital St Gallen, St Gallen, Switzerland, [10]Akershus University Hospital, Oslo, Norway, [11]Hôpital Saint-Antoine, Paris, France, [12]Toronto General Hospital, Toronto, Canada, [13]Centre Hôspitalier de l'Université de Montréal, Montréal, Canada, [14]Csapa Bizia, Bayonne, France, [15]South Riverdale Community Health Centre, Toronto, Canada, [16]Arud Centres for Addiction Medicine, Zurich, Switzerland, [17]St Vincent's Hospital, Sydney, Australia, [18]Footscray Hospital, Footscray, Australia, [19]Royal Adelaide Hospital, Adelaide, Australia, [20]Newcastle Pharmacotherapy Service, Newcastle, Australia, [21]Harm Reduction Victoria, Melbourne, Australia.

Disclosures

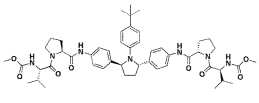
- Brian Conway has received honoraria, consultant fees and research funding from AbbVie, Gilead , Jannsen and Merck.
- Disclosures of all co-authors are available on file.

Background/rationale

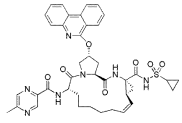
- Current/recent PWID account for 50% of prevalent and 75% of incident HCV infection in the developed world.
- Many current guidelines have identified PWID as a priority population to receive HCV treatment.
- PWID have had sub-optimal access to HCV treatment for a broad range of patient and provider-related factors.
- In some jurisdictions, ongoing drug use is still considered a relative or absolute contraindication to HCV treatment.

1) Grebely J, ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017 (FRI-236). 2) Grebely CID 2016. 3) Grebely CID 2016. 4) Grebely J, ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017 (FRI-235). 5) Zeuzem, S. Ann Intern Med 2015. 6) Dore, GJ Ann Intern Med 2016. 7) Grebely, Hajarizadeh, and Dore Nature Rev Gastro Hepatology 2017. 8) Norton B, et al. Int J Drug Policy In Press 2017; 9) Hull M, et al. INHSU 2016. 10) Conway AASLD 2016. 11) Bouscaillou EASL 2017. 12) Powis J. Int J Drug Policy 2017. 13) Read P. Int J Drug Policy 2017; 14) Litwin AL, et al. ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017; 15) Sulkowski M, et al. ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017. 16) Mazhnaya Int J Drug Policy In Press 2017. 17) Barua Ann Int Med 2017. 18) Ooka Am J Gastroenterol. 2017. 19) Marshall, AD et al. INHSU 2017, New York, United States, Sept 6-8, 2017.

Multi-Targeted 3 Direct-Acting Antiviral (3D) Regimen



Ombitasvir (OBV)
NS5A inhibitor



Paritaprevir (PTV)
NS3/4A protease inhibitor
boosted with ritonavir

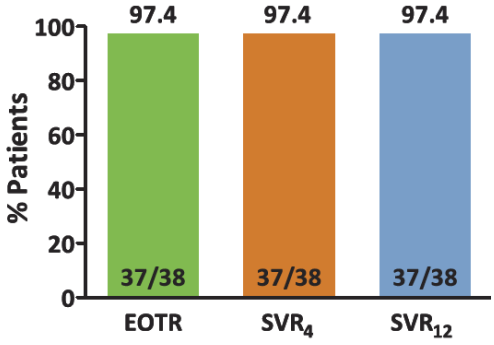
Dasabuvir (DSV)
non-nucleoside NS5B RNA
polymerase inhibitor

PTV was identified by AbbVie and Enanta

3D in people on OST

Parameter	3-DAA + RBV (N = 38)
Sex, male	25 (65.8)
Race	
White	36 (94.7)
Black	2 (5.3)
Hispanic or Latino ethnicity	1 (2.6)
Age, years ± SD	48.2 ± 11.0
BMI, kg/m² ± SD	27.0 ± 3.9
HCV RNA level, log_{10} IU/mL ± SD	6.58 ± 0.70
IL28B genotype CT or TT	26 (68.4)
Fibrosis stage	
F0–F1	30 (78.9)
F2	6 (15.8)
F3	2 (5.3)
HCV subgenotype 1a	32 (84.2)
Treatment-naive	36 (94.7)
Opioid replacement therapy	
Methadone	19 (50.0)
Buprenorphine	19 (50.0)

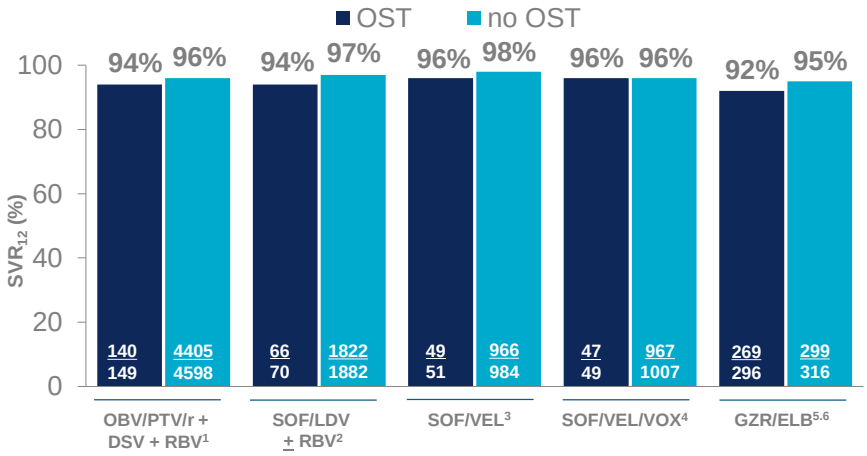
All values are n (%) unless otherwise noted.



- 37 of 38 patients (97.4%; 95% CI, 92.3–100) achieved SVR_4 and SVR_{12} **(Figure 2)**
- One patient prematurely discontinued due to a serious adverse event (cerebrovascular accident) unrelated to study drug (see Serious Adverse Events)
- There were no virologic failures

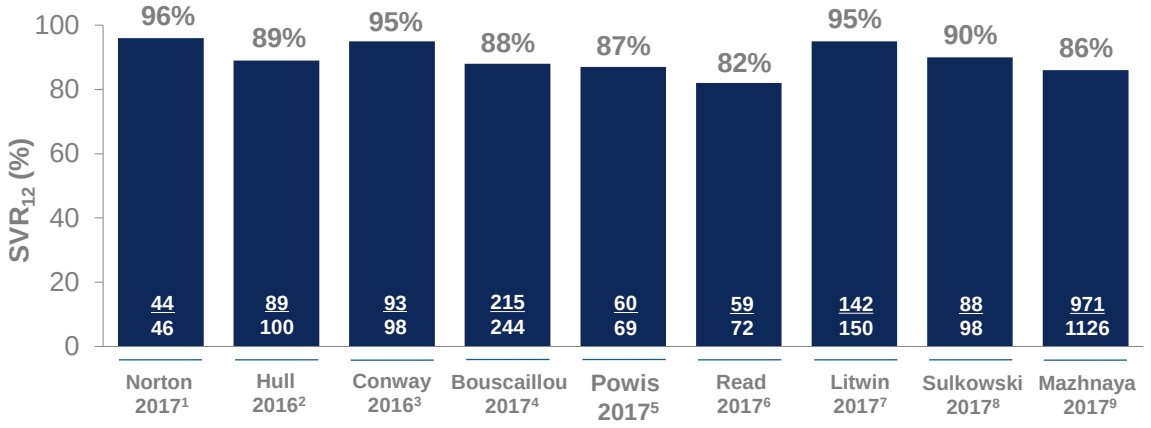
Lalezari J. J Hepatol. 2015;63(2):364-369.

People receiving OST – phase II/III trials



1) Grebely J, ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017 (FRI-236). 2) Grebely CID 2016. 3) Grebely CID 2016. 4) Grebely J, ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017 (FRI-235). 5) Zeuzem, S. Ann Intern Med 2015. 6) Dore, GJ Ann Intern Med 2016.

SVR12 among former/recent PWID



1) Norton B, et al. Int J Drug Pol 2017. 2) Hull M, et al. INHSU 2016. 3) Conway AASLD 2016. 4) Bouscaillou EASL 2017. 5) Powis J. Int J Drug Policy 2017. 6) Read P. Int J Drug Policy 2017; 7) Litwin AL, et al. ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017; 8) Sulkowski M, et al. ILC 2017, Amsterdam, The Netherlands, April 19-23rd, 2017. 16) Mazhnaya Int J Drug Policy In Press 2017.

Study Objectives

- To evaluate the efficacy and safety of a 12 week course of the combination of paritaprevir/ritonavir, ombitasvir and dasabuvir (with or without ribavirin) for the treatment of HCV genotype 1 infection among a population of individuals with current/recent injection drug use
- To monitor subjects for recurrent HCV viremia after the completion of successful HCV therapy (achievement of SVR12)

D3FEAT

Study Design

- Investigator-initiated, Kirby/UNSW sponsored, international open-label trial
- 19 sites, 7 countries
- Study recruitment conducted through a network of drug and alcohol clinics (n=4), hospital clinics (n=12), and community clinics (n=3)
- Participants enrolled between June 2016 and February 2017

D3FEAT

Study design and participant eligibility

D3FEAT

- DAA treatment-naïve patients with GT1 chronic HCV infection (F0-4)
- People receiving OST or with recent injecting drug use (past six months)
- Participants with HIV and decompensated liver disease excluded
- Participants received paritaprevir/ritonavir, ombitasvir, dasabuvir (3D) with (G1a) or without ribavirin (G1b) twice-daily using electronic blister packs to monitor adherence
- RBV: 1000 or 1200 mg daily according to body weight in 2 divided doses (<75 kg and ≥75 kg, respectively)

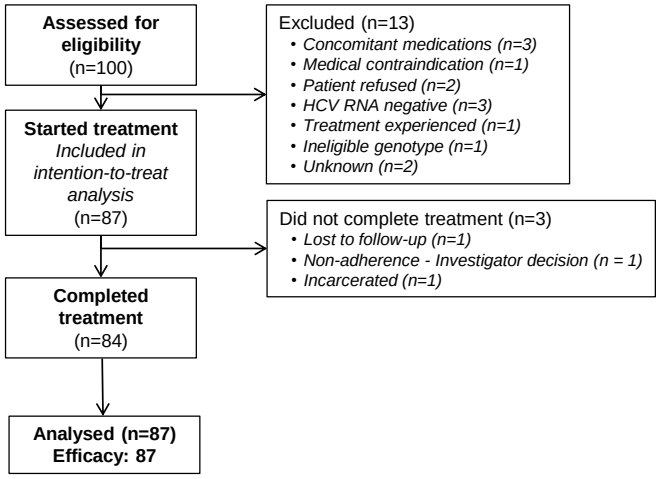
Study endpoints and statistical analysis

- SVR12 was the primary efficacy endpoint (intent-to-treat/modified ITT)
  - HCV RNA levels measured at certified local laboratories
  - Central testing (Hologic assay) is underway to confirm study endpoints
- Modified ITT was calculated excluding those lost to follow-up and/or not achieving SVR for reasons unrelated to HCV infection or its treatment
- Participants completed a self-administered questionnaire to collect information on demographics, drug and alcohol use, and injecting risk behaviours

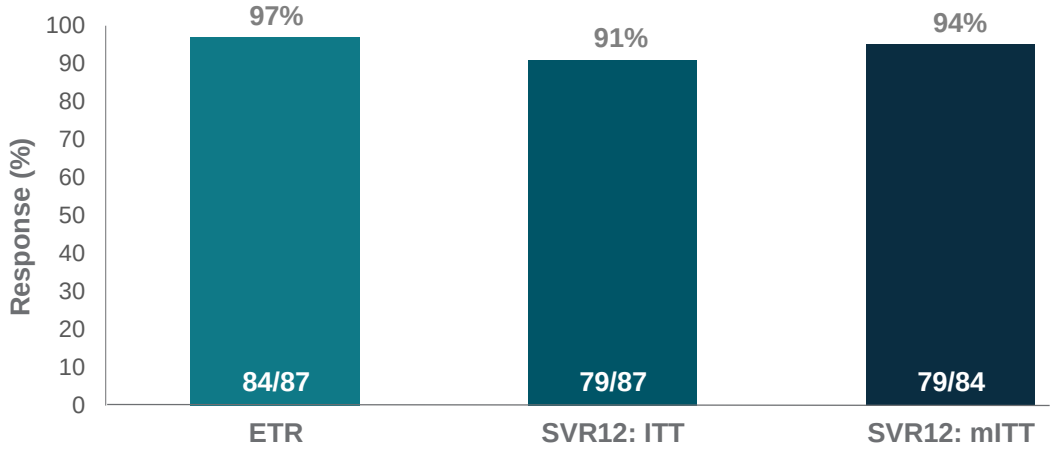
Participant characteristics

Characteristic	3D ± RBV (12 weeks) N = 87
Female, n (%)	23 (26%)
Age, median years (25%, 75%)	48 (43, 54)
Active injecting drug use (last 6 months), n (%)	50 (57%)
Current opioid substitution therapy, n (%)	69 (79%)
HCV genotype, n (%)	
1a	78 (90%)
1b	9 (10%)
Fibrosis stage (METAVIR), n (%)	
F0-F1	68 (78%)
F2-F3	12 (14%)
F4	7 (8%)
Study site distribution, n (%)	
Canada	38 (44%)
Europe	31 (36%)
Australasia	18 (21%)

Participant disposition



SVR12: Intent-to-treat



- 3 people lost to follow-up between ETR and SVR12
- 2 cases of viral relapse/reinfection (undergoing sequencing to distinguish)

SVR12 – Modified Intent-to-Treat Analysis

- ETR: 100% (84/84)
- ETR (SIMPLIFY): 100% (99/99)
- SVR12: 98% (79/81)
- SVR12 (SIMPLIFY): 99% (95/96)

- Loss to Follow-Up (n = 6)
- Absence of Cure (n = 2)

Methodological Issues

- SIMPLIFY and D3FEAT conducted sequentially at same/similar network sites
  - SIMPLIFY 04-10/16, 39/19/42% Canada/Europe/Australasia
  - D3FEAT 06/16 – 02/17, 44/36/21% Canada/Europe/Australasia
- D3FEAT recruitment affected by availability of commercial treatment options is some sites, but not others, accounting for different recruitment patterns
- Some sites where all treatment options were available were still able to recruit significant numbers of patients in D3FEAT
- Benefit of formally evaluating all available treatment options in this population

Methodological Issues

- SIMPLIFY: 74% active drug use, 60% OST
- D3FEAT: 57% active drug use, 79% OST
- C-EDGE CO-STAR: 25% active drug use, 100% OST

- Both SIMPLIFY and D3FEAT recruited a more vulnerable patient population with sufficient numbers of active drug users in both studies to validate the clinical use of both treatment options in the target population

- Data generated in more “real world” target populations, but from VERY EXPERIENCED SITES

Conclusions

- Among people receiving OST and those with recent PWID (past six months) with chronic HCV genotype 1 treated with 3D ± RBV, SVR12 was 91% on strict ITT analysis

- In a modified ITT analysis SVR12 was 98%

- Key patient characteristics (active drug use, lack of enrolment in OST program) did not affect treatment response

- There were no cases of virologic regimen failure

- These data provide further support for guidelines identifying PWID as a priority population to receive HCV therapy

Acknowledgements

I would like to particularly thank Amanda Erratt, the Study Co-ordinator for the D3FEAT study.

Protocol Steering Committee – Jason Grebely (Chair, UNSW Sydney, Sydney, Australia), Gregory Dore (UNSW Sydney, Sydney, Australia), Philippa Marks UNSW Sydney, Sydney, Australia), Olav Dalgard (Akershus University Hospital, Oslo, Norway), Philip Bruggmann (Arud Centres for Addiction Medicine, Zurich, Switzerland), Catherine Stedman (Christchurch Hospital, Christchurch, New Zealand), Karine Lacombe (Hôpital Saint-Antoine, Paris, France), Jeff Powis (South Riverdale Community Health centre, Toronto, Canada), Margaret Hellard (The Alfred Hospital, Melbourne, Australia) and Sione Crawford (Hepatitis Victoria, Melbourne, Australia).

Coordinating Centre – Amanda Erratt (Study Co-ordinator), Evan Cunningham (PhD Student), Behzad Hajarizadeh (Associate Lecturer), Gregory Dore (co-Principal Investigator), Jason Grebely (co-Principal Investigator), Pip Marks (Clinical Trials Manager), Ineke Shaw (Systems Manager), Sharmila Siriragavan (Data Manager) and Janaki Amin (Statistician).

Site Principal Investigators – Philip Bruggmann (Arud Centres for Addiction Medicine, Zurich, Switzerland), Patrick Schmid (Kantonsspital St Gallen, St Gallen, Switzerland), Erika Castro (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), Alberto Moriggia (Fondazione Epatocentro Ticino, Lugano, Switzerland), Karine Lacombe (Hôpital Saint-Antoine, Paris, France), Jean-Pierre Daulouede (Csapa Bizia, Bayonne, France), Olav Dalgard (Akershus University Hospital, Oslo, Norway), Brian Conway (Vancouver Infectious Diseases Center, Vancouver, Canada), Christopher Fraser (Cool Aid Community Health Centre, Victoria, Canada), Jeff Powis (South Riverdale Community Health Centre, Toronto, Canada), Jordan Feld (Toronto General Hospital, Toronto, Canada), Julie Bruneau (Centre Hôspitalier de l'Université de Montréal, Montréal, Canada), Curtis Cooper (The Ottawa Hospital, Ottawa, Canada), Ed Gane (Auckland Hospital, Auckland, New Zealand), Catherine Stedman (Christchurch Hospital, Christchurch, New Zealand), Gail Matthews (St Vincent's Hospital, Sydney Australia), Adrian Dunlop (Newcastle Pharmacotherapy Service, Newcastle, Australia), Margaret Hellard (The Alfred Hospital, Melbourne, Australia), Ian Kronborg (Footscray Hospital, Footscray, Australia) and David Shaw (Royal Adelaide Hospital, Adelaide, Australia).

Site Co-ordinators – Tina Horschik (Arud Centres for Addiction Medicine, Zurich, Switzerland), Simone Kessler and Cornelia Knapp (Kantonsspital St Gallen, St Gallen, Switzerland), Lorenza Oprandi (Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland), Paola Messina and Marzia Pantic (Fondazione Epatocentro Ticino, Lugano, Switzerland), Manuela Le Cam (Hôpital Saint-Antoine, Paris, France), Cecilia Maitre (Csapa Bizia, Bayonne, France), Jessica Andreassen, Ingunn Melkeraaen and Merete Moen Tollefsen (Akershus University Hospital, Oslo, Norway), Hannah Pagarigan (Vancouver Infectious Diseases Center, Vancouver, Canada), Rozalyn Milne (Cool Aid Community Health Centre, Victoria, Canada), Kate Mason (South Riverdale Community Health Centre, Toronto, Canada), Diana Kaznowski and Lily Zou (Toronto General Hospital, Toronto, Canada), Rachel Bouchard and Barbara Kotsoros (Centre Hôspitalier de l'Université de Montréal, Montréal, Canada), Miriam Muir and Jessica Milloy (The Ottawa Hospital, Ottawa, Canada), Victoria Oliver (Auckland Hospital, Auckland, New Zealand), Tracy Noonan (Christchurch Hospital, Christchurch, New Zealand), Alison Sevehon (St Vincent's Hospital, Sydney, Australia), Susan Hazelwood and Michelle Hall (Newcastle Pharmacotherapy Service, Newcastle, Australia), Michelle Hagenauer (The Alfred Hospital, Melbourne, Australia), Rachel Liddle (Footscray Hospital, Footscray, Australia) and Catherine Ferguson (Royal Adelaide Hospital, Adelaide, Australia).