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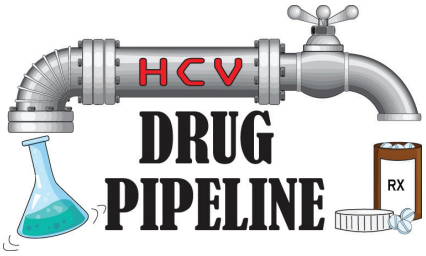

HCV Advocate Monthly Pipeline Update

A brief overview of how this pipeline is laid out:

Date: The Pipeline will be updated on a monthly basis and will be included with the HCV Advocate Newsletter.

Genotype (s): This lists the drugs or combination of drugs and the particular gentoype or genotypes that the drug is active against.

Comments: This section will list the study results. Within this section, I will list the genotype(s) being studied and the phase of the study with a brief recap of the study.

You will note that many of the drugs or combinations of drugs are pan-genotypic—that is they work on many or most of the HCV genotypes. **Note:** There is more detailed information about the drugs in development in our newsletter (http://hcvadvocate.org/publications/newsletter/) and our blog (http://hepatitisc.hcvadvocate.org/) and in the HCV Advocate Hepatitis C Drug Pipeline & Conference Coverage Site hcvdrugs.com

For EASL coverage see www.hcvdrugs.com

If you are interested in finding out about clinical trials visit HCV Advocate Clinical Trial Reference Guide (http://hcvclinical.hcvadvocate.org/) for a list of trials that are currently recruiting patients.

AbbVie	Genotype(s): 1, 2, 3, 4, 5, 6 (Pan-genotypic)

COMMENTS:
The combination of glecaprevir (ABT-493) plus pibrentasvir (ABT-530) to treat genotype 1, 3, 4, 5, 6 for a treatment duration of 8 weeks. The sustained virological results (SVR12/cure) released on 11/12/2016 are listed below:

Study Name	Patient Population	Treatment Duration	Treatment Regimen	SVR_{12} Rates
ENDURANCE-1	GT1 without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN +/- RBV or SOF/RBV +/- pegIFN), and patients co-infected with HIV-1	8 week	G/P	99% (348 of 351 pts)
ENDURANCE-3	GT3 without cirrhosis,new to treatment	8 week	G/P	95% (149 of 157 pts)
SURVEYOR-2 (Part 4)	GT2, 4, 5, or 6 without cirrhosis, new to treatment or not cured with previous IFN-based treatments (pegIFN, SOF/RBV orpegIFN/SOF)	8 week	G/P	97% (196 of 203 pts)

*pegINF = pegylated interferon; RBV= ribavirin; SOF=sofosbuvir;
This combination was granted Breakthrough Therapy designation by the Food and Drug Administration (FDA) for those with HCV genotype 1 who had failed a previous course of therapy that contained a NS5A inhibitor.
In December 2016 AbbVie applied to the FDA to market and treat all HCV genotypes with the combination listed above. On February 02, 2017 the FDA granted AbbVie Priority review for this combination.

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DRUG PIPELINE

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Gilead – Sofosbuvir, Valpatasvir& Voxilaprevir (GS-9857)	Genotype(s) 1,2,3,4,6, (Pan-genotypic)

COMMENTS:

Gilead released the results of four phase 3 studies (POLARIS) of the triple combination of sofosbuvir (polymerase inhibitor), velpatasvir (NS5A inhibitor), and voxilaprevir (protease inhibitor). The study included 1,056 patients who received the triple combination (sofosbuvir (SOF), velpatasvir(VEL), plus voxilaprevir (VOX)—611 were treatment naïve and 455 were treatment experienced.

Note: I am only listing the results from the triple therapy below – you will note that the percentage and numbers include all the patients treated. For a complete breakdown of all treatment regimens see November 2016 newsletter: http://hcvadvocate.org/news/NewsUpdates_pdf/Advocate_2016/advocate1116.pdf

Study	Population	Genotype	Treatment	Duration	SVR12 Rates
POLARIS-1	NS5A inhibitor-experienced 41 percent (172/415) had cirrhosis	1, 2, 3, 4, 5, 6	SOF/VEL/VOX	12 Weeks	96% (253/263)
			Placebo	12 Weeks	0% (0/152)
POLARIS-4	DAA-experienced (No NS5A inhibitor) 46 percent (153/333) had cirrhosis	1, 2, 3, 4	SOF/VEL/VOX	12 Weeks	97% (177/182)
			SOF/VEL	12 Weeks	90% (136/151
POLARIS-2	DAA-naïve 18 percent (174/941) had cirrhosis	1, 2, 3, 4, 5, 6	SOF/VEL/VOX	8 Weeks	95% (476/501)
			SOF/VEL	12 Weeks	98% (432/440)
POLARIS-3	DAA-naïve All had cirrhosis	3	SOF/VEL/VOX	8 Weeks	96% (106/110)
			SOF/VEL	12 Weeks	96% (105/109)

The side effects were similar between the placebo (sugar pills) group, sofosbuvir plus velpatasvir, and the sofosbuvir, velpatasvir plus voxilaprevir groups. The most common side effects were headache, fatigue, diarrhea and nausea. Only one patient in the entire study discontinued therapy due to side effects.

This combination was granted Breakthrough Therapy designation by the Food and Drug Administration (FDA) for those with HCV genotype 1 who had failed a previous course of therapy that contained a NS5A inhibitor.

In December 2016 Gilead applied to the FDA to market and treat all HCV genotypes with the combination listed above--combined into one pill taken once-a-day.

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DRUG PIPELINE

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Janssen (Achillion/Alios)	Genotype(s) 1,2,3,4,5,6 (Pan-genotypic)

EASL 2017: The results of the phase 2 study results of JNJ-4178 are included in the table below:

Dose			HCV Genotype	Dosing Duration (weeks)	Number (%) with undetectable HCV RNA at SVR24*
AL-335 (mg QD)	ODV (mg)	SMV (mg QD)			
400	50 QD	100	1	8	20/20 (100%)
800	50 QOD	75	1	8	20/20 (100%)
800	50 QOD	75	1	6	20/20 (100%)
800	50 QOD	—	1	8	21/25 (84%)
800	50 QOD	—	1	12	7/8 (88%)
800	50 QOD	75	3	8	0/5 (0%)
800	50 QOD	75	3	12	10/13 (77%)**

QD: every day; QOD: every other day; RNA: ribonucleic acid; SVR: sustained virologic response. *All results SVR24, with the exception of genotype 3 which is SVR12 **One patient did not attend SVR12 follow-up.

Note: The two drug combination of odalasvir and AL-335 for a treatment duration of 8 weeks will not proceed into phase 3 clinical trials. Clinical trial development of the combinations to treat HCV genotype 3 will also not move forward.

The combinations were generally safe and well-tolerated.

The next phase of development is to study these combinations in phase 2B studies.

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HCV DRUG PIPELINE

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Merck	Genotype(s) 1, 2, 3, 4, 5, 6 (Pan-genotypic)

COMMENTS:

- **Phase 2- AASLD 2016:**

C-Crest: The trial was a phase 2 study of a 3-drug co-formulation of MK-3682 (polymerase inhibitor), grazoprevir (protease inhibitor) plus ruzasvir (NS5A inhibitor) with and without ribavirin to treat HCV genotypes 1, 2 and 3. The treatment period was 8, 12 or 16 weeks. In the people who were previously treated with pegylated interferon plus ribavirin the SVR12/cure rates were 95% to 100% in genotype 1a, 1b and 3. In people with genotype 2 the cure rate was 87% in the 8-week group and a 100% rate in the 12-week group and 96% to 98% in the 16-week groups. There was very little difference in cure rates between the groups who had cirrhosis, and who did/did not receive ribavirin.

C-Surge: An on-going phase 2 study to treat people with genotype 1 who had failed a previous course of a direct-acting antiviral therapy (Harvoni or Zepatier) using MK-3682, grazoprevir and ruzasvir with and without ribavirin. In the group that received ribavirin the treatment duration was 16 weeks; in the group that did not receive ribavirin the treatment duration was 24 weeks. The cure rates were 98% (43 of 44 pts) in the 16 week group that received ribavirin and 100% (49 of 49 pts) in the 24 week group that did not receive ribavirin.

Regulus	Genotype(s) 1, 2, 3, 4, 6

COMMENTS:

Regulus has permanently canceled the development of RG-101.

Regulus Therapeutic Inc.

The study included 79 treatment-naive genotype 1 and 4 patients. RG-101 is a GalNAc-conjugated anti-miR targeting miR- 122, a host factor for HCV infection. It is an injectable medication given at Day 1 and Day 29 plus 4 weeks of a once-a-day direct-acting antiviral medication –Harvoni (27 patients), Olysio (27 patients), Daklinza (25 patients). Regulus issued a press release on June 7, 2016 that reported through 24 weeks of follow-up an additional 4 patients relapsed.

Time Since Treatment Completion	RG-101 + Harvoni	RG-101 + Olysio	RG-101 + Daklinza
Week 12	27/27 pts (100%)	26/27 pts (96.3%)	22/24 pts (91.7%)*
Week 16	21/21 pts (100%)	19/20 pts (95.0%)	20/22 pts (90.9%)
Week 20	14/14 pts (100%)	13/15 pts (86.7%)	13/13 pts (100%)
Week 24	10/10 pts (100%)	8/10 pts (80.0%)	8/9 pts (88.9%)

** One patient missed the Week 12 visit. Viral load results for this patient at week 8 and 16 were collected and indicate that the patient was a responder at both time points.*