Standard Response Letter for State Formulary Review ZEGALOGUE® (dasiglucagon) injection

PURPOSE

This Standard Response Letter has been prepared for you by Zealand Pharma US, Inc. It may include health care economic information, as defined under 21 USC 502(a) and FDA's final guidance on Drug and Device Manufacturer Communications with Payors, Formulary Committees, and Similar Entities (June 2018). The information is in no way intended to imply or suggest any claims regarding ZEGALOGUE® beyond its approved indication. Zealand Pharma is not responsible for the decisions you make based on the information presented.

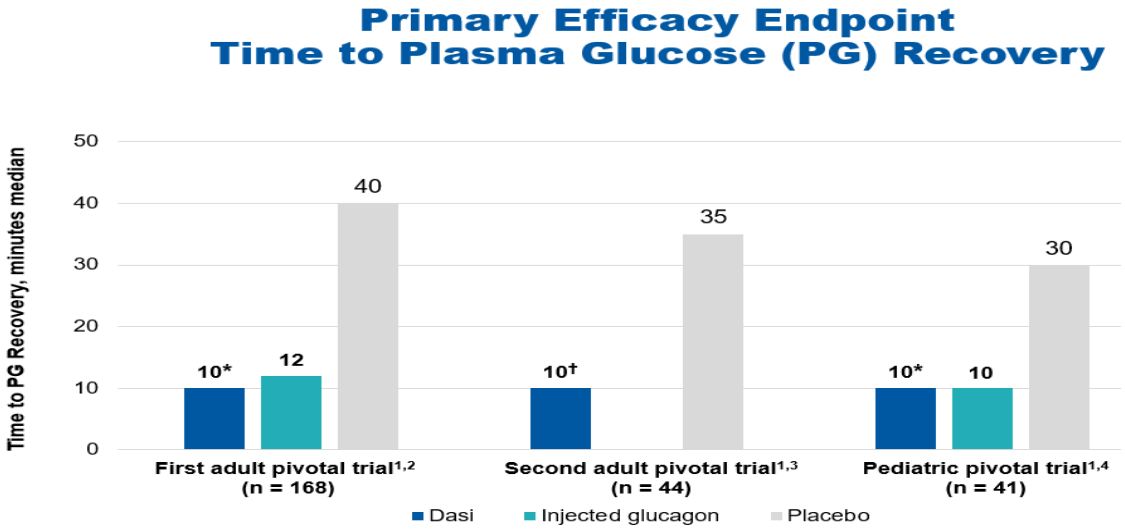
INTRODUCTION

ZEGALOGUE® (dasiglucagon) injection is a glucagon analog in aqueous formulation for subcutaneous dosing.[1] It is available in a ready-to-use formulation, not requiring reconstitution, – the single-dose autoinjector or a single-dose prefilled syringe – for the treatment of severe hypoglycemia in patients with diabetes aged 6 years and older.[1]

The efficacy and safety of dasiglucagon were evaluated in three pivotal phase 3, randomized, double-blind, placebo-controlled, multicenter trials in patients with type 1 diabetes mellitus (T1DM).[1] Two trials were conducted in adult patients (n=215) and one trial was conducted in pediatric patients aged 6 to 17 years (n=42).[2-4] The primary efficacy endpoint for all 3 trials was time to plasma glucose recovery (PG recovery) (treatment success) defined as an increase in blood glucose of ≥ 20 mg/dL from time of administration, without additional intervention.[2-4]

EFFICACY

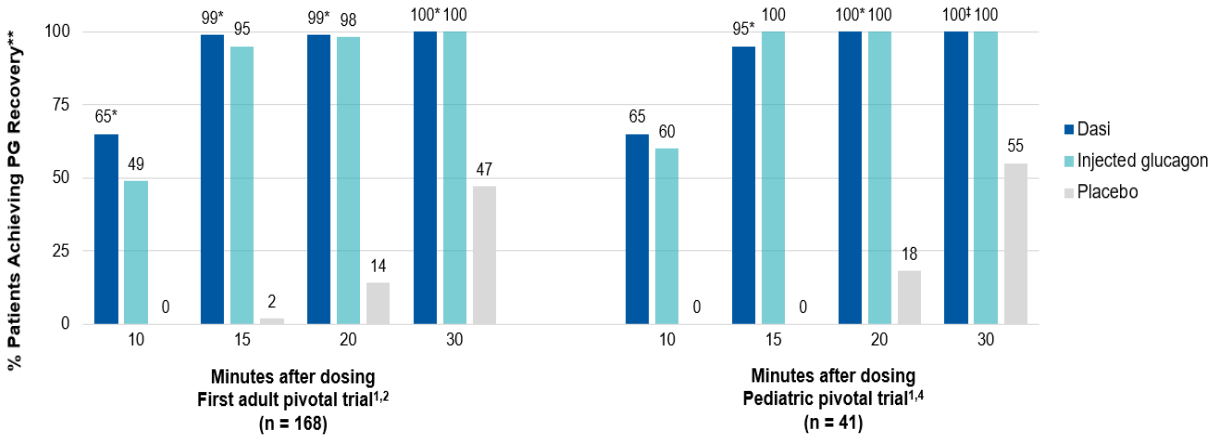
- Following controlled insulin-induced hypoglycemia, the median time to plasma glucose recovery was significantly faster with dasiglucagon treatment (10 minutes across all 3 trials) than with placebo treatment (range, 30-40 minutes; *p*< 0.001 dasiglucagon vs placebo for all comparisons).[1]



*p<0.001 dasiglucagon compared to placebo, †p<0.0001 dasiglucagon compared to placebo
Plasma glucose (PG) recovery = increase in plasma glucose of ≥ 20 mg/dL from time of administration
Reconstituted glucagon kit was used as a reference in this study
Data derived from full analysis set = patients who were randomized and treated

- In each trial, plasma glucose recovery at 10-, 15-, 20-, and 30-minutes posttreatment was achieved in a significantly greater proportion of patients in the dasiglucagon vs placebo groups.[2-4] Within the first 15 minutes post-dose, 99% of adults and 95% of pediatrics were recovered, respectively.[1]

Secondary Efficacy Endpoint
Percent of Patients Achieving Plasma Glucose (PG) Recovery



*p-values for comparison versus placebo statistically significant at all timepoints (p≤ 0.001), ‡p<0.01
In the second adult pivotal trial, 88% of patients achieved PG Recovery by 15 minutes (p≤ 0.001)
**Plasma glucose (PG) recovery = increase in plasma glucose of ≥ 20 mg/dL from time of administration
Reconstituted glucagon kit was used as a reference in this study
Data derived from full analysis set = patients who were randomized and treated

SAFETY RESULTS

- The most common adverse reactions (≥2%) associated with dasiglucagon in adults were nausea, vomiting, headache, diarrhea and injection site pain; in pediatrics: nausea, vomiting, headache and injection site pain.[1-4]

SUMMARY

- Across all 3 clinical trials (2 adult trials and the pediatric trial), a single subcutaneous dose of dasiglucagon 0.6 mg/0.6 mL resulted in plasma glucose recovery within a median of 10 minutes in patients with T1DM and insulin-induced hypoglycemia.[1]
- Dasiglucagon can be stored in a refrigerator for up to 36 months until the printed expiration date on the label. The product can also be stored at room temperature for up to 12 months or until the original expiration date, whichever comes first. Do not return dasiglucagon to the refrigerator after storing at room temperature.[1,5]
- Important safety information is provided on the following page.

IMPORTANT SAFETY INFORMATION

INDICATION

ZEGALOGUE (dasiglucagon) injection is indicated for the treatment of severe hypoglycemia in pediatric and adult patients with diabetes aged 6 years and above.

IMPORTANT SAFETY INFORMATION

Contraindications

ZEGALOGUE is contraindicated in patients with pheochromocytoma because of the risk of substantial increase in blood pressure and in patients with insulinoma because of the risk of hypoglycemia.

Warnings and Precautions

ZEGALOGUE is contraindicated in patients with pheochromocytoma because glucagon products may stimulate the release of catecholamines from the tumor. If the patient develops a substantial increase in blood pressure and a previously undiagnosed pheochromocytoma is suspected, 5 to 10 mg of phentolamine mesylate, administered intravenously, has been shown to be effective in lowering blood pressure.

In patients with insulinoma, administration of glucagon products may produce an initial increase in blood glucose; however, ZEGALOGUE administration may directly or indirectly (through an initial rise in blood glucose) stimulate exaggerated insulin release from an insulinoma and cause hypoglycemia. ZEGALOGUE is contraindicated in patients with insulinoma. If a patient develops symptoms of hypoglycemia after a dose of ZEGALOGUE, give glucose orally or intravenously.

Allergic reactions have been reported with glucagon products; these include generalized rash, and in some cases anaphylactic shock with breathing difficulties and hypotension. Advise patients to seek immediate medical attention if they experience any symptoms of serious hypersensitivity reactions.

ZEGALOGUE is effective in treating hypoglycemia only if sufficient hepatic glycogen is present. Patients in states of starvation, with adrenal insufficiency or chronic hypoglycemia may not have adequate levels of hepatic glycogen for ZEGALOGUE administration to be effective. Patients with these conditions should be treated with glucose.

Adverse Reactions

The most common adverse reactions (≥2%) associated with ZEGALOGUE in adults were nausea, vomiting, headache, diarrhea and injection site pain; in pediatrics: nausea, vomiting, headache and injection site pain.

Drug Interactions

Patients taking beta-blockers may have a transient increase in pulse and blood pressure when given ZEGALOGUE. In patients taking indomethacin, ZEGALOGUE may lose its ability to raise blood glucose or may produce hypoglycemia. ZEGALOGUE may increase the anticoagulant effect of warfarin**.**

Please see accompanying Full Prescribing Information

REFERENCES

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2. Pieber TR et al. Dasiglucagon: a next-generation glucagon analog for rapid and effective treatment of severe hypoglycemia results of phase 3 randomized double-blind clinical trial. *Diabetes Care* 2021;44:1–7. doi.10.2337/DC20-2995.
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4. Battelino T, et al. Dasiglucagon, a next-generation ready-to-use glucagon analog, for treatment of severe hypoglycemia in children and adolescents with type 1 diabetes: results of a phase 3, randomized controlled trial. *Pediatr Diabetes* 2021 May 2 doi: 10.1111/pedi.13220. Online ahead of print.
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EMPAVELI™ (pegcetacoplan) injection, for subcutaneous use
Apellis Pharmaceuticals
State Medicaid Testimony (submitted upon request)
Based on May 2021 FDA Label

This statement summarizes key information to support unrestricted access to pegcetacoplan, also known commercially as EMPAVELI for the treatment of adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

PNH: PNH is a rare, acquired, and potentially life-threatening hemolytic disease characterized by an attack on red blood cells by a component of the body's immune system called complement.[1] PNH impacts approximately 5,000 to 6,000 patients in the United States and is most frequently diagnosed in patients in their 30s.[2-5] When left untreated, patients with PNH have a 10-year mortality rate of 29% due to fatal complications such as thrombotic and hemorrhagic events[4]

Standard of care/unmet need: Currently, the standard of care for PNH are C5 inhibitors, including eculizumab and ravulizumab.[6] C5 inhibitors have improved patient survival by addressing intravascular hemolysis, yet despite this, many people with PNH continue to experience ongoing hemolysis and persistently low hemoglobin often requiring transfusions.[6-8] According to a retrospective study of patients treated with C5 inhibitors, 72% had persistently low hemoglobin and 36% required one or more transfusions.[9] The economic burden of transfusion dependent patients treated with C5 inhibitors can be substantial from a payer perspective. A claims-based analysis assessing the real-world economic impact of PNH found that transfusion dependence was associated with approximately $220,000 higher annual direct medical costs per patient compared to PNH patients who were transfusion free.[10] There is a need for additional therapies for PNH to address these challenges.

EMPAVELI: EMPAVELI is a complement inhibitor indicated for the treatment of adult patients with PNH.[11] EMPAVELI contains a BOXED WARNING regarding the risks of meningococcal and other serious infections caused by encapsulated bacteria (similar to the BOXED WARNINGS for the C5 inhibitors). Patients should be vaccinated according to ACIP recommendations prior to starting therapy. The product is only available through a REMS program.[11] Refer to the full prescribing information for complete safety information including boxed warning, contraindications, warnings & precautions, and adverse reactions.

MOA and administration: EMPAVELI binds to complement protein C3 and C3b, acting proximally in the complement cascade to control both intravascular and extravascular hemolysis in PNH.[11] Unlike available C5 inhibitors, EMPAVELI can be self-administered by the patient as a subcutaneous infusion twice weekly.[11]

Clinical Trials: The safety and efficacy of EMPAVELI in PNH has been assessed in a phase 3 randomized, open-label, head-to-head study compared to eculizumab in patients who continued to experience hemoglobin levels less than 10.5g/dL despite receiving a stable dose of eculizumab.[11-12] EMPAVELI was superior to eculizumab on the primary endpoint of change from baseline in hemoglobin level with an increase of 2.37g/dL versus a decrease of 1.47 g/dL with eculizumab, demonstrating an adjusted mean increase of 3.84g/dL compared with eculizumab at week 16.[11-12] Additionally, EMPAVELI met non-inferiority on the key secondary endpoints of transfusion avoidance and change from baseline in absolute reticulocyte count. 85% of patients in the EMPAVELI arm and 15% of patients treated with eculizumab remained transfusion free at week 16.[11-12] From a safety perspective, the most common adverse reactions were injection site reactions, infections, diarrhea, abdominal pain, respiratory tract infection, viral infection and fatigue.[11] Apellis has also conducted studies in patients with PNH who did not previously receive C5 inhibitors. Increases in hemoglobin were observed in these trials.[11]

In summary, EMPAVELI provides a treatment option with the potential to improve hemoglobin levels in all adult patients with PNH over current standard of care. We respectfully ask the committee to add EMPAVELI to formulary to provide unrestricted access for patients with PNH.

References:

1. Borowitz MJ, Craig FE, DiGiuseppe JA, et al. Guidelines for the diagnosis and monitoring of paroxysmal nocturnal hemoglobinuria and related disorders by flow cytometry. *Cytometry Part B Cytom*. 2010;78(4):211-230.
2. Hill A, Platts PJ, Smith A, et al. The incidence and prevalence of paroxysmal nocturnal hemoglobinuria (PNH) and survival of patients in Yorkshire. *Blood*. 2006;108(11):985.
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5. de Latour RP, Mary JY, Salanoubat C, et al. Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories. *Blood*. 2008;112(8):3099-3106.
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8. Hill A, DeZern AE, Kinoshita T, et al. Paroxysmal nocturnal hemoglobinuria. *Nat Rev Dis Primers.* 2017;3(17028).
9. McKinley CE, Richards SJ, Munir T, et al. Extravascular hemolysis due to C3-loading in patients with PNH treated with eculizumab: defining the clinical syndrome. *Blood*. 2017;130(suppl 1):3471
10. Cheng WY, et al. Real-world treatment patterns and healthcare resource utilization (HRU) of patients with paroxysmal nocturnal hemoglobinuria (PNH) receiving eculizumab in a US population. Poster presented at: American Society of Hematology Annual Meeting; December 2020.
11. EMPAVELI [package insert]. Waltham, MA: Apellis Pharmaceuticals; 2021
12. Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. *N Engl J Med* 2021; 384:1028-1037.

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October 27, 2021

Mr. Roger Citron
OSU College of Pharmacy – DURM
OHA Health Systems Division
500 Summer St. NE, E35
Salem, OR 97301

Re: Public Testimony: Request for Review of Truvada for PrEP Indications
Recommendation for Preauthorization to fix non-evidence-based Risk Assessment
Addressing problems in OHA PrEP policies.

Dear Mr. Citron:

I am a Portland based activist and occasional medical journalist. In 2014-2017 I reported critically on the PrEP indicator trials, and in 2021, I published an article critical of PrEP and OHA policies in the *Portland Tribune.* I have over twenty years of experience in AIDS activism, and I have no conflicts of interest with any pharmaceutical company. I ask this communication be presented to the P/T Committee. I am writing to urge the adoption of a level of preauthorization review for PrEP indications to ensure safe evidence-based use.

According to Oregon's 2020 Prescription Drug Transparency Act report, Truvada is the 4th most expensive specialty drug. The report called the drug one of the most costly due to its PrEP indication. In June this year, the legislature passed HB 2958B allowing pharmacists to dispense Truvada directly. The bill disallowed preauthorization requirements for private insurers, but this did not extend to the OHP. Truvada has substantial toxicities and there have been no long-term clinical trials evaluating its impact on clinical endpoints. My research indicates PrEP is being widely dispensed beyond FDA-indications to individuals for which there is no evidence to support its use. Furthermore, the drug industry is paying full-time "PrEP Navigators" to be employed at Oregon AIDS Service organizations whose job it is to increase Truvada sales charged to the Oregon Health Plan. The Oregon Health Authority also provides factually incorrect information on its website about PrEP's safety and efficacy. The net effect of these policies is to overtreat and cause net harm.

When the FDA approved PrEP in 2012 after the payment of a $710,000 "user fee" by Gilead, it indicated a vaguely-defined "other individuals at risk" category in an advisory panel vote of 12-8 with two abstentions. The problem is that bias, misconceptions, regulatory capture, can lead to prescriptions for individuals who are not actually at risk and to individuals for which there is no evidence to support the efficacy of PrEP use.

1. No Controlled Clinical Trial Data for PrEP Effectiveness in Injection Drug Users

An example would be PrEP dispensed to active injecting drug users, and OHA documents indicate this population is being targeted for PrEP promotion. **The Food and Drug Administration made no evaluation of controlled clinical trials to determine efficacy in this population**, and a transcript of the Advisory Panel indicates members were concerned about **lack of evidence**. Through 2019, all PrEP prescribers were required to complete a Risk Evaluation and Management Strategy (REMS) education course to be educated on this point. I enclose the FDA's own documents stating there is no evidence of PrEP effectiveness from controlled clinical trials. The OHA publicly states that PrEP is "71% effective" for injection drug users, but it gives no citation. This comes from a single desperately flawed study that was insufficiently controlled to demonstrate efficacy.

PrEP research emphasizes adherence, and any active injecting drug user with the capacity to adhere to regular HIV testing, filling prescriptions, and taking the drugs routinely as directed is also capable of filling a prescription

for sterile injection equipment and using it routinely. Injection drug users are very likely to be on Medicaid, so it seems that the **more cost-effective prophylaxis based in evidence is to prefer dispensation of sterile syringes on the formulary**. I question the wisdom of dispensing drugs to drug users, as impure street drugs can combine and interact to create all sorts of unexpected toxicities. Unfortunately, Gilead Sciences is making direct contributions through is FOCUS program to the state's needle exchanges, meaning "PrEP Navigators" affiliated with the exchanges are pushing Truvada instead of common sense and evidence-based care. One exchange at Portland's Central City Concern even has an in-house pharmacy to robo-prescribe the drugs.

As somebody who has volunteered to work with injection drug users, I often heard the claim that they didn't understand how they became HIV positive as they always used sterile equipment. I've also been confused by the paradox that healthcare worker exposure seroconversion is nonexistent (something that cannot be fully ascribed to PEP) but injection drug user seroconversion is common – even when the reported modes of transmission are identical. I researched the issue, and it turns out there are problems with the HIV tests when used in injection drug using population. This was proven in the best-designed study of HIV and Needle Exchange Programs by Julie Bruneau in Montreal – where exclusive sterile injection equipment users were 22 times more likely to seroconvert. This paradoxical result evidences a dirty little secret about the HIV ELISA: it was designed in 1984 as a double-test for screening blood donations: both screening for HIV antibodies but also screening for probable injection drug use. This is disclosed in a single sentence in the National Cancer Institute's patent for the test from April 23, 1984 and in a 1987 report by the World Health Organization.

In the 70's and 80's prior to the advent of recombinant biotechnologies to produce gamma globulins and clotting factors, it was common for blood product manufacturers to purchase "donated" blood – often from impoverished individuals. It was impractical to test blood for recreational substances, and there was a desire to screen out donors with a history of injected drug use – many of whom would not admit to it. The NIH realized that injected drug users often had hypergammaglobuanemia, so when constructing the HIV ELISA, they added a test for elevated antibodies to p41 which is the ubiquitous cellular protein actin. The French, who first "discovered" HIV in 1983 did not characterize what they called LAV with p41 or Actin and they said this was a contaminant. The test was designed before HIV had even been isolated (via molecular cloning) in December 1984. In 1994, British Virologist Robin Weiss (who developed the British ELISA using the CEM cell line rather than the clone of HUT-78) admitted to *Sunday Times* reporter Neville Hodgkinson that the American "HIV Test" also had this secret drug-use-screening function. The UK test does not include p41, and this is why injection drug users in the UK don't test positive anywhere near the rates in the US.

Had the FDA reviewed the NIH HIV test which was licensed to Abbot Labs and sold to the American Red Cross, it would not have passed validation studies. HHS Secretary Margaret Heckler simply announced on April 2, 1985 that the FDA had approved the test. There was no staff examination of the data or advisory panel meeting. The FDA only approved the ELISA as a screening test, and the FDA official who was finally hired to review the new test, Thomas Zuck, admitted in 1986 to a panel of the World Health Organization that it was premature but impractical to recall the test. Every generation of HIV test that has been approved has not been validated against HIV – they've been validated against the previous generation going all the way back to the flawed 1985 test. This wasn't necessarily a problem because the FDA demanded a more specific confirmatory test that would help rule out false positives. This provided for blood donor screening out of drug users but prevented misdiagnosis.

In 2014, the CDC issued new screening algorithm guidelines that seem crafted to manufacture false positives by withdrawing the confirmatory antibody test and replacing it with a PCR or bDNA Nucleic Acid test. Here's the problem: impure street drugs injected directly to the bloodstream can cause toxic shocks causing the expression of novel RNA or the expression of endogenous human retroviruses – including HERV-K and HERV-W which cross-react with the Nucleic Acid Tests, misinterpreted by clinicians as "HIV-1 Viral Load." It's unclear if anyone at the CDC remembered that the HIV-ELISA had a secret double purpose, but the algorithm change in this context does explain why officials are perceiving increased injection-drug-use-associated "transmission."

2. Generic Viread may be more cost-effective than Generic Truvada

Truvada is FTC/TDF, whereas Viread is just TDF. The claimed active ingredient in Truvada is Tenofovir (TDF), and all the early PrEP indicator trials tested Viread.

The reason why Gilead applied to the FDA for an expanded use authorization for Truvada but not Viread in 2012 was FTC went off patent in 2021 and TDF went off patent in 2016. Therefore, the only reason why FTC is included in both Truvada as well as Descovy is that Gilead wanted to get four additional years of exclusive marketing. The second ingredient introduces additional marginal toxicities.

OHP could consider generic Viread as a formulary-preferred option if it is cheaper.

3. Oregon's "Risk Categories" for PrEP indications are not based in evidence

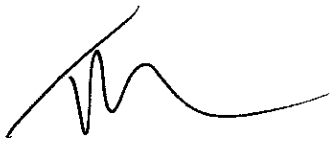
The OHA-commissioned 2017 "PrEPWorks" report really reads like a marketing document, but it identifies individuals who are "at risk" per the FDA's vague indication that are not actually "at risk"

- Sex Workers: the comprehensive AIDS literature indicates that the only commercial sex workers at risk for HIV seroconversion are those who use recreational drugs.
- "Men who have sex with Men" – just being gay or practicing gay sex is not enough. The FDA only indicated PrEP for "High Risk Gay Men," which has subsequently been defined and is rather arbitrary. The reality is that official guidelines state it takes over 1000 HIV sexual exposures to result in HIV seroconversion.
- "Persons who are sexually active and use condoms sparingly" – Heterosexual transmission is so rare as to be nonexistent, and the most extensive study (MACS) indicate the only sexual act correlated to HIV seroconversion is frequent passive anal intercourse with ejactulation. Public Health surveillance staff will privately admit they don't believe in "HetCons" and report mode of transmission as "indeterminate."
- "Patients over 50 who have multiple sex partners" – this seems like a way to gin up customers with good insurance and has nothing to do with risk.
- "Blacks" – African Americans are targeted for testing, as a consequence, they are misperceived as a risk group due to the color of their skin. The reality is Blacks have a stronger antigenic response, and are likely to have false positives on HIV tests. The CDC acknowledged the problem in 2006.

In Conclusion

Reigning in the unchecked rollout of PrEP in Oregon to a more evidence based approach will both save taxpayer funds and improve health outcomes. In the years since PrEP's approval, annual Oregon seroconversions have declined by about 15 annually – something that can't be attributed to PrEP, yet over 6000 individuals who are not sick are being treated. This is a terrible "Number Needed to Treat." The "standard of care" for seroconversion is to be put on ARV's anyway, so not taking PrEP reduces the total lifetime toxic load. Moreover, PrEP leads to reduced condom use raising incidence of other STI's, and there are no good long-term studies on clinical endpoints demonstrating whether PrEP produces net benefit or net harm. Pharmacist-prescribed PrEP opens the door to self-risk-assessment that is not accurate leading to unnecessary overtreatment of "worry warts" who are not actually "at risk." PrEP dispensed to injection drug users is likely to compound toxicities of impure recreational street drugs and dispensation of sterile injection equipment is a far cheaper method of risk reduction.

I am happy to present my research and make an in-person presentation.



Thomas J. Busse

Flaws in the PrEP Indicator Trials:

- Suspect "early termination" could be strategic once a statistical blip was maintained and indicate unblinding.
- Far too short to control for study-entry effects. Far too short in general.
- Funding by Gates/NIAID meant that failed trial data didn't have to be shown to FDA, yet Gates is an investor ($3B+) in Gilead.
- Small USA centers for iPREX added at the last minute outside the original trial design.
- iPREX multi-center raises red-flags, as it is a common source of fraud in drug trials.
- P/R for VOICE and FemPREP indicated "low adherence" was the cause – but the trial was big enough there should have been a difference even among those who adhered should the medication have been effective. In 2017, the STRAND study came out regarding VOICE showing adherence was normal. There may be a metabolism issue regarding TDF and bioavailability falsely blamed by researchers as "bad adherence." FDA never saw these trials.
- Buried in the iPREX supplementary appendix (pg 33) is a disclosure about "occult seroconversion" and "preexisting seroconversions" – and that these were only in the Truvada cohort. This indicates possible fraud to throw out data in order to achieve significance or investigator bias in interpreting test results.
- No long-term follow-up to determine true seroconversions. This is a problem in African HIV trials because of common cross-reactions. Africans reverse-seroconvert quite often, but this is censored in the medical literature
- Whatever happened to HIV-2?
- Seroconversion rate is WAY TOO HIGH. Compare PARTNERS to the Padian Study which observed zero seroconversions in a 160 partner cohort in Northern California over ten years.
- iPREX is too short – some participants were enrolled for only 5 months
- No controls for recreational drug use, meaning risk categories are uncontrolled.
- No clinical endpoints, and the HIV seropositivity surrogate marker is not a guarantee of progression to AIDS in the risk groups studied.

Context:

Discussions of PrEP started with the 2002 approval of Viread, and in 2008, the evidence to support ARV surrogate markers fell apart. In 2012, the international AIDS conference returned to the USA in an election year, and the industry was desperate to have a victory.

PrEP represents BILLIONS of dollars in new market drug sales and investigators in the indicator trials disclosed multiple conflicts of interest. Postmarket observation that adherence correlates to low seropositivity could also reflect adherence as an indicator of comprehensive risk reduction and not Truvada efficacy.

Comparison of the Four Major PrEP Trials (From document research by Terry Michael, as of May 31, 2014.)

Name of trial, funding source/s, drugs used.	Number of subjects in trial. Description and size of cohorts.	Geographical location/s*** of subjects.	Time frame of study and report release date.	Findings claimed by investigators	Alternative view of what the data demonstrate.
iPREX PrEP NIAID & Gates F. Truvada# /TDF-FTC Placebo	2,499 total MSM* All HIV- Truvada =1,251 Placebo = 1,248 2/5 prostitutes	Peru (56%) plus Ecuador, Brazil, Thailand, S. Africa, US (9% SF/Boston) ***91% 3rd World***	Enrolled between July '07 - Dec. '09; halted early May '10 Article NEJM+ 12/30/10	Truvada =36 Sero-Conv. Placebo =64 Sero-Conv. formula^: 64-36/64 = 44% claimed as greater protect. than placebo	97% of Truvado cohort ***did not*** sero-conv.; 95% of placebo cohort ***did not*** sero-conv. **2% *"better"* with drugs?** Buried in report is claim 90% + better for absolute adherence.##
Partners PrEP Gates F. Viread#/TDF Truvada# /TDF-FTC Placebo	4,747 hetero *couples*, sero-discordant** Viread=1,584 Truvada = 1,579 Placebo = 1,584	Kenya and Uganda ***100% 3rd world***	Enrolled between July'08-Nov.'10 halted early, 5/31/11 Article NEJM 8/2/12	Viread x=17 (67%) Truvada x=13 (75%) Placebo = 52 formula^: 52-x/52 = % claimed "more protected"	99% of drugged cohorts did not sero-conv. 97% of placebo cohort did not sero-conv. **2% *"better"* with drugs?**
~~**Fem-PrEP**~~ ~~Gates F. & USAID~~ ~~Truvada#/TDF-FTC~~ ~~Placebo~~	2,120 female HIV- Truvada=1,024 Placebo = 1,032 (had planned 3,900)	South Africa, Kenya, Tanzania ***100% 3rd world***	Enrollment began 2009, **halted 4/2011** Halting explained CROI# March 2012	Truvada = 33 (3.2% Sero-C.) Placebo = 35 (3.4% Sero.C) "Protection" statist. **identical** formula: x/cohort size	96.8% Truvada cohort and 96.6% of placebo cohort did not sero-conv. **two-tenths of 1% "better"?**
~~**VOICE PrEP**~~ ~~NIAID~~ ~~Truvada#/TDF-FTC~~ ~~Viread#TDF; Viread gel~~ ~~Placebo tabs & gel~~	5,029 female HIV- Truvada=994; Viread=1002; Viread gel=1003; placebo tab=1008; placebo gel=1003	South Africa (80%), Uganda, Zimbabwe ***100% 3rd world***	Enrollment between 9/'09 - 6/'11; **halted 10/2011.** Halting explained CROI 3/'13	Sero-C's:Truv.=61, Viread =60, placebo tabs=60. ***Equal*** "protection." Viread gel=61, placebo gel=70; statist. insig. difference	94% Truv., 94% Viread and 94% placebo tab cohorts did not Sero.C. 94% Viread gel and 93% placebo gel did not Sero-C. 1% **"better"?**

NOTES.....

NIAID = Nat. Institute of Allergy and Infectious Diseases; Gates F. = Bill and Melinda Gates Foundation;
USAID = U.S. Agency for International Development. Truvada = TDF-FTC = tenofovir disoproxil fumarate and emtricitabine.
Viread = TDF = tenofovir disoproxil fumarate. Drugs are chemotherapy, called "anti-retroviral treatments" or ARVs or ARTs.

# Gilead donated ALL drugs used in all trials ~~X~~ = HALTED when results didn't match conf. biases of investigators	*MSM = Men who have Sex with Men. ** 1 partner HIV+ and 1 HIV-	*** All funded by U.S. entities, with U.S. drugs, seeking U.S. FDA approval, yet almost 100% 3rd world subjects??	#Conf. on Retroviruses and Opportunistic Infections +New England Journal of Medicine	^ Placebo sero-con.'s minus drug sero-con's divided by placebo Sero-Cs = % "less" sero-con. than placebo	##This 90%+ is a non-real world condition of not missing single dose, yet news stories cite it instead of already spurious 44%

NOTE: iPREX trial (gay men,) and Partners PrEP (hetero discordant couples) were at the heart of Gilead's effort to obtain "fast-track" FDA approval for Truvada for HIV *negatives*. Paying a "user fee," Gilead got 6-month action -- a "fast track"-worthy emergency use for non-"positive," non-ill individuals, for a drug retailing $12-$14,000/year? Even orthodox HIV experts warn against "premature" use of toxic chemicals in *positives*, because of adverse effects over time to liver, kidney and heart, meaning 10 or 15 years, often less. None of the PrEP trials lasted much more than a year or two. Thus, there was no evidence on long-term adverse effects in negatives. The trials were a collusion between Gilead, NIAID, FDA and CDC, which put its stamp of approval on prescription of Truvada for PrEP in May 2014. It was all about the money, subjecting gay men, IV drug users, 3rd world people, and African Americans (the "risk groups") to lethal chemotherapy.

FDA REMS Document

Question 2 Correct answer: B	**Which of the following statements is false?** a) Emtricitabine/tenofovir disoproxil fumarate should be used for a PrEP indication only in individuals confirmed to be HIV-1 negative b) Emtricitabine/tenofovir disoproxil fumarate has been found to be safe and effective for pre-exposure prophylaxis to reduce the risk of acquiring HIV-1 infection through injection drug use c) Women taking Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication should not breastfeed their babies d) Emtricitabine/tenofovir disoproxil fumarate for a PrEP indication is not always effective in preventing HIV-1 infection **Correct** Next *[Advances to next screen]* **Incorrect. Please try again.** Try again *[Greys out selected wrong answer]*
Question 3 Correct answer: B	**Which of the following items are not included on the Checklist for Prescribers for initiating Emtricitabine/Tenofovir Disoproxil Fumarate for a PrEP indication?** a. Perform HBV screening test b. Perform testing for TB c. Confirm negative HIV-1 status of the individual d. Confirm creatinine clearance is ≥60 mL/min **Correct** Next *[Advances to next question]* **Incorrect** Try again *[Greys out selected wrong answer]*

Figure 23: Most costly drugs

Drug	Drug class	Amount spent
Humira	Analgesics - Anti-Inflammatory	$80,509,117
Enbrel	Analgesics - Anti-Inflammatory	$33,771,085
Stelara	Dermatologicals	$23,399,682
Truvada	Antivirals	$20,608,725
Biktarvy	Antivirals	$18,042,219
Rituxan	Antineoplastics And Adjunctive Therapies	$16,983,505
Cosentyx	Dermatologicals	$15,746,169
Herceptin	Antineoplastics And Adjunctive Therapies	$14,072,476
Remicade	Gastrointestinal Agents	$13,635,198
Opdivo	Antineoplastics And Adjunctive Therapies	$13,532,849

Source: Oregon Prescription Drug Price Transparency Program

As mentioned above, three of the drugs on this list – Humira, Enbrel, and Truvada – were also among the most frequently prescribed specialty drugs in 2019. Between Humira and Truvada, both of which treat autoimmune disorders including rheumatoid arthritis, reporting insurers paid $114,280,202 in claims in 2019. Between Truvada and Biktarvy, used in the treatment of HIV/AIDS, insurers paid $38,650,944 in claims. Finally, the three most costly cancer drugs on this list, which are typically the most expensive on a per-patient basis, cost Oregon insurers more than $44,588,830 in claims.

Figure 24: Most costly generic drugs

Drug	Used to treat	Amount spent by insurance companies
Amphetamine Dextroamphetamine	Narcolepsy and ADHD	$6,223,708
Methylphenidate	ADD and ADHD	$6,175,683
Buprenorphine	Opioid dependence	$4,435,548
Levothyroxine	Thyroid	$3,742.458
Estradiol	Estrogen	$2,979,520

Source: Oregon Prescription Drug Price Transparency Program

This final chart, showing the five most costly generic prescriptions in Oregon, has almost zero overlap with the most prescribed or most expensive per prescription lists, with the exception of the thyroid agent levothyroxine, which was the most prescribed generic drug in Oregon with 231,684 prescriptions in 2019.

Health insurance companies

The program requires health insurance companies to report on prescription drugs in Oregon. Health insurance companies are required by state law to report the 25 most prescribed drugs, the 25 most costly drugs, and the 25 drugs that caused the biggest increases in yearly health plan spending in the 2019 calendar year.

For 2020, we provided additional instructions to carriers to produce more consistent data across reporting insurers, due to inconsistencies in how reports were filed in 2019. Our analysis of insurer data in 2019 was also supported by information shared from the All-Payer All-Claims (APAC) database maintained by the Oregon Health Authority. For 2020, we directly asked reporting insurers for several more pieces of data for each drug, including the number of prescriptions issued, the number of enrollees affected, and the total amount of plan spending on each drug (net of rebates and other price concessions). With this additional information, we have been able to conduct more comprehensive analysis without relying on APAC data.

While we believe this has led to an overall more accurate set of data, it is also much more limited, since the program currently receives reports only from companies that sell plans on the state's individual and small group insurance marketplaces. These companies are the only ones required to report to the program. Less than 50 percent of the insurance market is represented in this data. It does not include most group health insurance, Medicare, or government sponsored insurance. For 2020, lists were received from all 10 health insurance companies required to file:

- BridgeSpan Health Company
- Health Net Health Plan of Oregon
- Kaiser Foundation Health Plan of the Northwest
- Moda Health Plan
- PacificSource Health Plans
- Providence Health Plan
- Regence BlueCross BlueShield of Oregon
- Samaritan Health Plans
- UnitedHealthcare Insurance Company
- Cigna Global Health Service Company

Due to our changes in data collection methodology for insurer reports between 2019 and 2020, the data is not directly comparable between the two years of the program, and our analysis is limited to information reported by insurers in 2020. The program released several aggregated lists based on our insurer reports last month, and the underlying data is available on our website.

Most prescribed drugs

The tables below were created using aggregated data across the lists submitted by all 10 reporting insurers in 2020. The most frequently prescribed generic drug in 2019 was levothyroxine, a treatment for hyperthyroidism, with 231,684 prescriptions across our 10 reporting insurers, while the most frequently prescribed brand-name drug was the seasonal flu vaccine with 342,608 prescriptions. This represents multiple NDCs and manufacturers for each compound.

The most prescribed specialty drugs in 2019 included Humira with 17,435 prescriptions and Enbrel with 7,986 prescriptions. Both products are anti-inflammatory drugs used in the treatment of autoimmune diseases such as rheumatoid arthritis. Also notable on this list is Truvada, most well known for its use for Pre-Exposure Prophylaxis ("PrEP") to prevent the transmission of HIV to sexual partners. All three of these drugs were also among the most costly for Oregon's insurers in 2019.

Lines blurred between HIV health message, marketing

MYVIEW

By Tom Busse

BUSSE

Pharmaceutical company Gilead Sciences is broadcasting "PrEP Up Step Up" television ads in the Portland media market.

"PrEP" stands for Pre-Exposure Prophylaxis — a new trend of prescribing daily chemotherapy to HIV-negative gay men in a belief this will prevent HIV seroconversion. As of 2018, 5,011 Oregonians were prescribed PrEP charged to various taxpayer-funded programs at a retail price of $1,800 a month. This represents about $108,200,000 in public funds annually accruing to Gilead Sciences to buy drugs for people who are not sick.

I recently downloaded and logged in to a gay "hook-up app." Of the first 16 men on the app, 15 disclosed, "I am taking PrEP."

As a former activist with ACT-UP, I had been skeptical of PrEP since its rushed 2012 FDA approval. In markets where PrEP use has increased, public health departments are seeing an uptick in sexually transmitted infections in gay men — especially syphilis. This indicates PrEP is substituting for condoms. The FDA's PrEP indications are limited to "high-risk gay men" who are required to be counseled in comprehensive risk reduction (i.e. told to use condoms).

Unlike the ads on the television, the Oregon Health Authority's website mentions nothing about side effects. This is a problem in public health messaging because it blurs the line between pharmaceutical marketing and patient education. Oregon's major AIDS service organizations receive funding from PrEP's manufacturer, and The Lund Report indicates pharmaceutical manufacturers put $277,000 into Oregon political campaigns.

Until 2019, the FDA prohibited Gilead from advertising PrEP due to an FDA "Risk Evaluation and Mitigation Strategy"; therefore, Gilead turned to third parties such as the Cascade AIDS Project to promote the drugs. These are "Black Box Drugs" meaning when taken at normal doses, they can be lethal, because they have killed others. Public health agencies are not required to disclose black box conditions and side effects on their websites. They are also not required to be accurate in safety and efficacy claims.

To illustrate the problem: The websites of the Cascade AIDS Project and the Oregon Health Authority claim PrEP is "96% Effective." The website of the Oregon HIV Alliance states PrEP "can reduce the risk of sexually acquired HIV infection by more than 90%." The training materials of the Oregon AIDS Education & Training Center state, "PrEP is more than 90% effective at preventing HIV."

The FDA-approved package insert states: "In a key controlled clinical trial (PrEP) was shown to reduce the risk of HIV-1 infection acquisition by 42% for high risk men who have sex with men who also received comprehensive prevention services."

Gilead makes no efficacy claims on television. Two placebo-controlled studies (VOICE and FEMPrEP) conducted before PrEP's approval but published five years later found PrEP to be completely ineffective. The 96% statistic came from the CDC website, which looked at uncontrolled Gilead-funded observational studies.

Drug efficacy can only be determined through placebo-controlled clinical trials, and the Oregon Administrative Rule 581-022-1440 requires OHA and publicly funded non-governmental organizations' health education materials be "medically accurate" and base their statements on the scientific method — true placebo-controlled trials of the type reviewed by the FDA.

The difference between 42% efficacy and 96% efficacy is considerable, and it can lead to risky behavior or a false sense of security. As a matter of policy, public service messaging about drugs really should conform to FDA marketing standards.

Still, in the context of a quick hook-up on an app, who really looks at the package insert to read, "the long term effects of (PrEP) are unknown"?

Tom Busse of Northwest Portland is an activist with Multnomah Librarians and formerly with ACT-UP/Golden Gate.