UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

DIVISION OF
CORPORATION FINANCE

February 27, 2014

Via E-mail
Thomas E. Hughes, Ph.D.
President and Chief Executive Officer
Zafgen, Inc.
One Broadway, 8th Floor
Cambridge, MA 02142

Re: Zafgen, Inc.
Confidential Draft Registration Statement on Form S-1
Submitted January 31, 2014
CIK No. 0001374690

Dear Dr. Hughes:

We have reviewed your confidential draft registration statement and have the following comments. In some of our comments, we may ask you to provide us with information so we may better understand your disclosure.

Please respond to this letter by providing the requested information and either submitting an amended confidential draft registration statement or publicly filing your registration statement on EDGAR. If you do not believe our comments apply to your facts and circumstances or do not believe an amendment is appropriate, please tell us why in your response.

After reviewing the information you provide in response to these comments and your amended confidential draft registration statement or filed registration statement, we may have additional comments.

General

1. Please submit all outstanding exhibits as soon as practicable. We may have further comments upon examination of these exhibits.

2. Please provide us proofs of all graphic, visual or photographic information you will provide in the printed prospectus prior to its use, for example in a preliminary prospectus. Please note that we may have comments regarding this material.

3. Please supplementally provide us with copies of all written communications, as defined in Rule 405 under the Securities Act, that you, or anyone authorized to do so on your behalf, present to potential investors in reliance on Section 5(d) of the Securities Act,

whether or not they retain copies of the communications. Similarly, please supplementally provide us with any research reports about you that are published or distributed in reliance upon Section 2(a)(3) of the Securities Act of 1933 added by Section 105(a) of the Jumpstart Our Business Startups Act by any broker or dealer that is participating or will participate in your offering.

4. We note that your exhibit index indicates you have submitted an application for confidential treatment covering several of your exhibits. We will deliver comments to your confidential treatment request under separate cover.

Business
Severe Obesity in the General Population, pages 77-78

5. We note your disclosure of current treatments for severe obesity and their "key limitations." Below this table, you should include the qualification that beloranib could also be subject to some of the same limitations for treatment of obesity. In this regard, we note that one of the treatments is limited by unpleasant gastrointestinal side effects, which have also been observed as adverse events in clinical trials for beloranib. We also note your disclosure on page 89 that you expect beloranib will carry a Category X label and be contraindicated in pregnant women or women looking to become pregnant, which is another key limitation included in the chart on page 78. Please revise accordingly. In addition, please clarify the specific meaning of the key limitation, "potential for abuse," and disclose whether the same limitation could apply to beloranib.

Clinical Trials, page 81

6. We note your statement on this page that you conducted additional clinical trials of beloranib to "further explore the efficacy, safety, tolerability and impact" of the drug on obesity. However, we also note your disclosures on pages 5 and 88 that none of your clinical trials were designed to "demonstrate efficacy." However, you describe at least two of your trials as "Phase 2b" clinical trials, which are usually designed to assess, at least in part, efficacy. Further, we note descriptions of endpoints in multiple of your clinical trials that would seem to relate to measurements of efficacy, including endpoints relating to weight loss and body composition. As such, it is unclear how investors should properly assess, and how much weight to accord, any clinical observations from these trials that bear on efficacy. Please clarify any inconsistencies. For example, please revise your disclosure in this section to address the following:

- the primary clinical endpoints for each trial and the extent to which the endpoints were met;

- how secondary objectives, such as weight loss or changes in body composition, were analyzed (e.g., as part of the intended trial design or on a post-hoc basis); and

- to what extent, if any, you may rely on results from trials conducted to date in your regulatory filings with the FDA to support claims of efficacy if the trials were not designed to demonstrate efficacy.

Please ensure that you are consistent throughout disclosure on these points.

7. Please include in your disclosure a brief discussion of the importance and use of statistical significance in clinical trial analytics. Please also provide an explanation of "p-values" in layman's terms and put this terminology in context by disclosing the threshold p-value below which a clinical result would be viewed as statistically significant.

4-week Phase 1b Proof of Concept Clinical Trial in Obese Patients (ZAF-101), page 85

8. We note your disclosure that at the highest dose, beloranib appears to be less tolerated and leads to more frequent moderate intensity TEAEs. Please disclose the frequency with which the referenced TEAEs occurred in this trial.

Phase 2a Clinical Trials
ZAF-201, page 86

9. We note your bullet points in this section stating that levels of the inflammation marker C-reactive protein and sense of hunger were both reduced. Please clarify:

    - the relevance of low concentrations of C-reactive protein and the relationship, if any, of inflammation to obesity.

    - how sense of hunger corresponded to measurements of cm and mg and how such measurements were obtained

ZAF-211, pages 87-88

10. We note your disclosure that changes in body weight were "not statistically significant by ANCOVA, a pre-specified statistical analysis." As this is not term that is familiar to non-specialists, please briefly define ANCOVA, explain how it was used in the analysis of trial results, and disclose whether it was considered in regard to all endpoint measurements.

11. We note your disclosure that "engagement of the underlying drug pathway occurs with beloranib treatment in PWS patients, as evidenced by the treatment-related increase in high density lipoprotein cholesterol [and] the reduction in low density lipoprotein cholesterol." Please clarify this statement by explaining why high density and low

density lipoprotein cholesterol levels suggest engagement of the underlying drug pathway and the significance of this effect to beloranib's potential as an effective treatment.

Clinical Trial Summary and Next Steps, pages 88-89

12. We note that you are currently designing a Phase 2b/3 clinical trial to support registration and commercialization of beloranib in PWS patients. Please disclose generally the primary clinical objectives of this planned trial. To the extent known, please describe the clinical trial's design and goals, including primary clinical endpoints to be measured.

13. For your planned Phase 2b/3 clinical trial of beloranib in PWS patients, please elaborate on your strategy for patient enrollment. Approximately how many patients do you expect you will require for successful completion of this trial? How do you expect to find and enroll the PWS patients, and what difficulties do you anticipate, if any? In this regard, we note the rarity of the disease and the fact that only 17 PWS patients were enrolled in the ZAF-211.

14. We note your disclosure that you plan to seek feedback from the FDA in early 2014 before initiating further clinical trials. Please disclose what sort of feedback you will seek and disclose whether you will require anything specific, such as a Special Protocol Assessment, from the FDA before moving forward with further trials for beloranib.

Licenses
CKD License, page 91

15. Please disclose the potential aggregate amount of milestones you may be required to pay under this agreement.

Children's License, page 91

16. Please disclose the nature of the patents covered by this agreement. For example, do they provide different protection than those covered under the CKD license? If so, what type of protection do they provide? In addition, please disclose the potential aggregate amount of milestones you may be required to pay and the termination provisions governing this license. Finally, please file this license agreement as an exhibit to your registration statement.

Intellectual Property, pages 91-92

17. We note that the issued U.S. patents directed to beloranib are expected to expire between 2019 and 2031. Please disclose the specific year of expiration for your composition of matter patent(s) covering beloranib, and disclose whether you own or license such patent(s).

18. Please revise to clarify the distinction between "international" and "foreign" patent applications.

19. Given your plan to pursue development and commercialization of beloranib in Europe, please disclose which of your issued or pending international and foreign patents afford protection in Europe. Include disclosure of the expiration date or expected expiration date of the most significant patent(s) applicable to Europe. Please additionally include an explanation of any material European/international patent laws and regulations and how they may affect your intellectual property position.

Government Regulation
European Union Drug Review and Approval, page 103

20. We note your disclosure on page 99 that the benefits of orphan drug status in the European Union are almost identical to the benefits in the U.S. To the extent material differences exist between the U.S. and European regulatory process with respect to orphan drugs, please revise disclosure on page 103 to describe the criteria for and process of seeking orphan drug designation in Europe.

Director Compensation, page 116

21. Please confirm that you will file as an exhibit to your registration statement the nonemployee director compensation agreement that will become effective upon the completion of this offering.

Shares Eligible for Future Sale
Lock-up Agreements, page 133

22. Please file the form of lock-up agreement as an exhibit to your registration statement as soon as it becomes available.

Market and Industry Data and Forecasts, page 144

23. Please note that it is not appropriate to state or imply that you do not have liability for the statements in your registration statement. Your statements in this section that the accuracy and completeness of the information is not guaranteed and that you have not independently any of the referenced data could imply that you are not taking liability for the statistical and other industry and market data included in your registration statement. In order to eliminate any inference that you are not liable for all of the information in your registration statement, please delete these statements or include a statement specifically accepting liability for these statements.

If you intend to respond to these comments with an amended draft registration statement, please submit it and any associated correspondence in accordance with the guidance we provide in the Division's October 11, 2012 announcement on the SEC website at http://www.sec.gov/divisions/corpfin/cfannouncements/drsfilingprocedures101512.htm.

Please keep in mind that we may publicly post filing review correspondence in accordance with our December 1, 2011 policy (http://www.sec.gov/divisions/corpfin/cfannouncements/edgarcorrespondence.htm). If you intend to use Rule 83 (17 CFR 200.83) to request confidential treatment of information in the correspondence you submit on EDGAR, please properly mark that information in each of your confidential submissions to us so we do not repeat or refer to that information in our comment letters to you.

You may contact Christine Torney at (202) 551-3652 or Jim Rosenberg at (202) 551-3679 if you have questions regarding comments on the financial statements and related matters. Please contact Austin Stephenson at (202) 551-3192, Dan Greenspan at (202) 551-3623, or me at (202) 551-3715 with any other questions.

Sincerely,

/s/ *Daniel Greenspan for*

Jeffrey P. Riedler
Assistant Director

cc: Via E-mail
Michael J. Minahan, Esq.
Goodwin Procter LLP