Reviewer #1: Drug induced pancreatitis is scarcely reported in literature for several reasons. TIP has been a major hurdle in managing patients with IBD. I appreciate authors' attempt to study this under-reported and clinically relevant entity. 1. The study hypothesis is a novel approach to this issue. Authors collected and summarized all the information available. Their experience in this field has been clearly reflected in the manuscript. 2. Using patient specific iPSCs may be future of studying ADRs especially drug induced pancreatitis as current literature is solely dependent on case reports 3. Major limitation is the very limited number of study objects. However as this concept is evolving and complexity of methods, its reasonable to accept the findings 4. I would appreciate and curious to see if authors can mention the cost-effectiveness of this method.

Reply: We thank the reviewer for the feedback on our paper. As requested we mentioned the cost-effectiveness of this innovative method and in particular we added the following sentence in the manuscript:

"The cost of hospitalization after a pancreatitis event has been recently calculated resulting in around 8,000 € per patient [27]. Considering an incidence of 5% we can estimate that every 20 patients treated with azathioprine one will be at risk of pancreatitis. Therefore, to be cost effective the analysis should figure at 400 €, considering only the cost of the analysis without evaluating the health benefit [28]. Current costs are still higher but there is a trend toward reduction indeed, the iPSC technology is still expensive and costs have to be reduced before they can be introduced into clinical practice. In particular, characterization costs are high but several suggestions to address this limitation have been already proposed such as SNP microarray technology for the routine karyotyping and cost-effective methods such as innovative flow cytometry analysis to assess cell surface expression of pluripotent markers [29] " .

Reviewer #2: This editorial on Induced pluripotent stem cells as an innovative model to study drug induced pancreatitis the authors have highlighted the importance of induced pluripotent stem cells (iPSCs) in investigating the cellular and molecular mechanisms underlying the development of this thiopurine induced pancreatitis (TIP). By this new idea researchers will be able to understand the mechanism behind TIP. The quality and

importance of this editorial is appropriate. The conclusions are appropriately summarised the editorial. The key problem in this field is availability of pancreatic tissue for research, which will possibly be solved by using iPSC. There are some syntax and grammatical errors, needs to be corrected, like sentences should not be started with abbreviations.

Reply:

We appreciate the consideration that the reviewer gave to our manuscript. The manuscript has been checked for grammatical and syntax errors and abbreviations at the beginning of sentences have been removed.

Reviewer #3: - Table 1 is a relevant addition. - Recommend adding figures to further illustrate sequence of differentiating HES into pancreatic exocrine cells. This reviewer found it useful to review figures from Ref #16 for a relevant representation of the process. - Consider delving deeper into the discussion with regards to the terminal differentiation of pancreatic exocrine cells. o Some of the cited references comment on the question of endocrine vs exocrine activity. o An important (general) question in the process of terminal differentiation is if the amylase markers are sufficient to reflect terminal differentiation. The discussion mentions some improvement in the differentiation protocol to distinguish between acinar and ductal cell types. Some expansion on the implications thereof in ensuring terminal differentiation would be as representative/close as possible to in vivo models may help complete the argument.

Reply:

We thank the referee for his comments. As suggested, we added a figure representing iPSC differentiation into pancreatic exocrine cells to further illustrate differentiation steps. We agree with the reviewer that an important point is if the amylase markers are sufficient to reflect terminal differentiation. Beside studies considering the mRNA level of these markers more functional studies should be implemented evaluating the amylase protein concentrations and enzyme activity. These comparisons would allowed to ensure that terminal differentiation would be as representative as possible of in vivo models. These considerations were added in the "PATIENT-SPECIFIC INDUCED PLURIPOTENT STEM

CELLS AS AN IN VITRO MODEL TO STUDY DRUG-INDUCED PANCREATITIS" section:

"An important point to consider is if the amylase markers are sufficient to reflect terminal differentiation. Beside studies considering the mRNA level of these markers [24,25] more functional studies should be implemented evaluating the amylase protein concentrations and enzyme activity. These comparisons would allowed to ensure that terminal differentiation would be as representative as possible of in vivo models."

Reply to science editor:

Thank you for your consideration. We answered to reviewers, we corrected the minor language syntax and grammatical errors and, as requested, removed one of the three self-citation to respect the self-referencing rates of less than 10% and attached the approved grant application form.