

# Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with nontransfusion-dependent thalassemia syndromes

Ali T Taher<sup>1</sup>  
John B Porter<sup>2</sup>  
Antonis Kattamis<sup>3</sup>  
Vip Viprakasit<sup>4</sup>  
M Domenica Cappellini<sup>5</sup>

<sup>1</sup>Department of Internal Medicine, American University of Beirut, Beirut, Lebanon;

<sup>2</sup>Department of Haematology, University College London, London, UK;

<sup>3</sup>First Department of Pediatrics, University of Athens, Athens, Greece;

<sup>4</sup>Department of Pediatrics and Thalassemia Center, Siriraj Hospital, Mahidol University, Bangkok, Thailand;

<sup>5</sup>Department of Internal Medicine, Università di Milano, Ca Granda Foundation IRCCS, Milan, Italy

## Dear editor

As the scientific steering committee for THALASSA (an assessment of Exjade in nontransfusion-dependent thalassemia [NTDT]), we read with interest the review by Kontoghiorghes and Kontoghiorghes entitled “Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes” published in January 2016.<sup>1</sup> While this review provides a detailed overview of available iron chelators for the treatment of NTDT patients, there remain some factual inaccuracies and misrepresentations of data related to deferasirox. Therefore, we believe that the current article may be misleading to readers of *Drug Design, Development and Therapy*.

Foremost, there is no mention that to date deferasirox is the only oral iron chelator approved for the treatment of chronic iron overload in NTDT patients. Approval was granted following the successful THALASSA trial (n=166), the first randomized, controlled study showing that deferasirox significantly reduces iron overload in NTDT patients with a manageable safety profile.<sup>2,3</sup> As such, we feel that the recommendation by Kontoghiorghes and Kontoghiorghes for deferiprone as the first-line treatment of NTDT patients is concerning given the absence of robust clinical evidence and regulatory approval. Indeed, deferiprone is recommended as a second-line treatment in most clinical practice guidelines worldwide. Furthermore, the authors draw many of their conclusions regarding deferasirox tolerability from postmarketing surveillance information, yet neglect to mention premarketing clinical trial experience from ~700 adult/pediatric patients supporting a clinically manageable safety profile for deferasirox with appropriate patient monitoring.<sup>4</sup> Both sources of data should be considered for a balanced analysis of drug-related tolerability issues.

There are also several specific claims regarding deferasirox that we would like to highlight as inaccurate and provide further supportive evidence to the contrary:

- “DFX appears to increase iron and other toxic metal absorption.” Concerns about the increased iron uptake were addressed during the development of deferasirox and were shown not to occur.<sup>5</sup> Given the structural similarities between iron–deferasirox and aluminum–deferasirox complexes,<sup>6</sup> increased gastrointestinal uptake of aluminum would not be anticipated in vivo. These data were neither discussed nor cited.

Correspondence: Ali T Taher  
Department of Internal Medicine,  
American University of Beirut, Riad El  
Solh 1107 2020, Beirut, Lebanon  
Email ataher@aub.edu.lb

- “[...] excess iron removal from the heart by DFX is not effective and in most cases very slow, with no improvement in LVEF, especially in heavily iron-loaded TM patients.” Clinical evidence for deferasirox in the removal of cardiac iron has been demonstrated in the large, prospective EPIC cardiac substudy and the randomized CORDELIA study.<sup>7,8</sup> Deferasirox was effective in removing cardiac iron and maintaining cardiac function in thalassemia patients with mild, moderate, and severe cardiac siderosis. Furthermore, in CORDELIA, although the enrolled patients had left ventricular ejection fraction  $\geq 56\%$  at baseline, small improvements were noted in some patients.<sup>8,9</sup> This is important because even small improvements can reduce the risk of heart failure.<sup>10</sup>
- “The use of DFX is not recommended for iron-loaded patients with serum ferritin lower than 500 ng/mL.” The authors cite deferasirox-labeling information from 2010, prior to updates in 2015 that include the indication of deferasirox for NTD patients. In the 2015 version, treatment interruptions are indicated when serum ferritin is  $< 300$  ng/mL, the safety of which was established in THALASSA.<sup>4,11</sup>
- “Lower efficacy and higher toxicity was reported for DFX in TI [...] by investigators not related or funded by the manufacturers of DFX.” This statement is based on one retrospective, single-center study of a combined population of  $\beta$ -thalassemia major and intermedia patients.<sup>12</sup> The cited study by Karimi et al<sup>13</sup> was an independent study, and there are additional investigator-initiated studies<sup>14,15</sup> that were not cited. Together with the outcomes of THALASSA, results from these studies provide credible evidence supporting the efficacy and safety of deferasirox in NTD patients.
- “DFX is also very expensive and cannot be afforded by the vast majority of patients.” Here, there is no mention of cost-effectiveness analyses by Karnon et al<sup>16</sup> who have demonstrated that the higher drug cost of deferasirox may be offset by savings due to the cost of DFO administration (eg, pumps and needles) or the reduced need to treat iron overload-related complications that can develop when patients are not compliant with DFO.

Finally, we feel it necessary to inform readers that Dr Kontoghiorghes has a conflict of interest in deferiprone, which has not been declared. Dr Kontoghiorghes was a member of the team who first synthesized deferiprone and has subsequently been described as the discoverer (eg, <http://www.pri.ac.cy/research.htm>).

We hope this letter clarifies some of the misconceptions presented by Kontoghiorghes and Kontoghiorghes and will provide physicians with additional information for consideration when deciding upon the most appropriate treatment for their patients.

## Acknowledgments

The THALASSA trial was funded by Novartis Pharma AG. We thank Rebecca Helson, PhD, of Mudskipper Business Ltd for medical editorial assistance. Financial support for medical editorial assistance was provided by Novartis Pharmaceuticals Corporation.

## Disclosure

ATT reports receiving research funding and honoraria from Novartis. JBP reports consultancy, receiving research grant funding and honoraria from Novartis, consultancy and honoraria from Shire, and consultancy for Celgene. JBP is supported by the NIHR University College London Hospitals Biomedical Research Centre (BRC). AK reports participation in advisory boards and educational forums sponsored by Novartis and Apopharma and receiving research funding from Novartis. VV received research grant support and lecture fees from Novartis, Genzyme-Sanofi, Sebia, and Roche Diagnostics and research grant support from Shire, Sideris and Faculty of Medicine, Siriraj Hospital, Thailand. MDC reports receiving honoraria from Novartis, Genzyme, and Celgene. The authors report no other conflicts of interest in this work.

## References

1. Kontoghiorghes CN, Kontoghiorghes GJ. Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes. *Drug Des Devel Ther*. 2016;10:465–481.
2. Taher AT, Porter J, Viprakasit V, et al. Deferasirox significantly reduces iron overload in non-transfusion-dependent thalassemia: 1-year results from a prospective, randomized, double-blind, placebo-controlled study. *Blood*. 2012;120(5):970–977.
3. Taher AT, Porter JB, Viprakasit V, et al. Deferasirox effectively reduces iron overload in non-transfusion-dependent thalassemia (NTDT) patients: 1-year extension results from the THALASSA study. *Ann Hematol*. 2013; 92(11):1485–1493.
4. Novartis Pharmaceuticals [webpage on the Internet]. EXJADE® (deferasirox) US Prescribing Information; 2015. Available from: <http://www.pharma.us.novartis.com/product/pi/pdf/exjade.pdf>. Accessed August 31, 2016.
5. Nick H, Wong A, Acklin P, et al. ICL670A: preclinical profile. *Adv Exp Med Biol*. 2002;509:185–203.
6. Steinhäuser S, Heinz U, Bartholoma M, et al. Complex formation of ICL670 and related ligands with Fe<sup>III</sup> and Fe<sup>II</sup>. *Eur J Inorg Chem*. 2004; 21:4177–4192.
7. Pennell DJ, Porter JB, Cappellini MD, et al. Efficacy of deferasirox in reducing and preventing cardiac iron overload in  $\beta$ -thalassemia. *Blood*. 2010;115(12):2364–2371.

8. Pennell DJ, Porter JB, Piga A, et al. A 1-year randomized controlled trial of deferasirox versus deferoxamine for myocardial iron removal in beta-thalassemia major (CORDELIA). *Blood*. 2014;123(10):1447–1454.
9. Westwood MA, Anderson LJ, Maceira AM, et al. Normalized left ventricular volumes and function in thalassemia major patients with normal myocardial iron. *J Magn Reson Imaging*. 2007;25(6):1147–1151.
10. Pennell DJ, Carpenter J-P, Roughton M, Cabantchik IZ. On improvement in ejection fraction with iron chelation in thalassemia major and the risk of future heart failure. *Cardiovasc Magn Reson*. 2011;13:45.
11. Taher AT, Porter JB, Viprakasit V, et al. Approaching low liver iron burden in chelated patients with non-transfusion-dependent thalassemia: the safety profile of deferasirox. *Eur J Haematol*. 2014;92(6):521–526.
12. Al-Khabori M, Bhandari S, Al-Huneini M, Al-Farsi K, Panjwani V, Daar S. Side effects of deferasirox iron chelation in patients with beta thalassemia major or intermedia. *Oman Med J*. 2013;28(2):121–124.
13. Karimi M, Arandi N, Haghpanah S, et al. Efficacy of deferasirox (Exjade(R)) in modulation of iron overload in patients with beta-thalassemia intermedia. *Hemoglobin*. 2015;39(5):327–329.
14. Ladis V, Berdousi H, Gotsis E, Kattamis A. Deferasirox administration for the treatment of non-transfusional iron overload in patients with thalassaemia intermedia. *Br J Haematol*. 2010;151(5):504–508.
15. Voskaridou E, Plata E, Douskou M, et al. Treatment with deferasirox (Exjade) effectively decreases iron burden in patients with thalassaemia intermedia: results of a pilot study. *Br J Haematol*. 2010;148(2):332–334.
16. Karnon J, Tolley K, Oyee J, Jewitt K, Ossa D, Akehurst R. Cost-utility analysis of deferasirox compared to standard therapy with desferrioxamine for patients requiring iron chelation therapy in the United Kingdom. *Curr Med Res Opin*. 2008;24(6):1609–1621.

## Author's reply

George J Kontoghiorghes

Postgraduate Research Institute of Science, Technology, Environment and Medicine, Limassol, Cyprus

Correspondence: George J Kontoghiorghes  
Postgraduate Research Institute of Science, Technology, Environment and Medicine, 3 Ammochostou Street, Limassol 3021, Cyprus  
Tel +357 2627 2076  
Email kontoghiorghes.g.j@pri.ac.cy

## Dear editor

There are many murky areas and marketing, legal, ethical, and other conflicts in the pharmaceutical industry, some of which involve physicians and academics. These activities and related ethical issues affect the safety and treatment of millions of patients.<sup>1–11</sup> Irregular and sometimes illegal activities for new patented drugs carried out by pharmaceutical companies, such as secrecy agreements with academics/academic institutions, can lead to biased reporting of the results of clinical trials and cover ups or underreporting of toxic side effects, as well as doctor's bribes, irregularities in drug pricing, corruption of the drug regulatory authorities, influential medical journals and patient organizations, etc.<sup>1–11</sup> The commercial influence and drug marketing tactics by pharmaceutical companies in the case of deferasirox affect the safety and long-term survival of thousands of thalassemia and other categories of transfused patients.<sup>11–14</sup>

Misinformation on Exjade has recently reached the stage of criminal investigations and fines, eg, of US \$60 million settlement of a civil fraud lawsuit for understating life-threatening toxicities and US \$45 million for false claim allegations being submitted to federal health care programs.<sup>15–17</sup> Furthermore, one of the largest law suits ever faced by a pharmaceutical company of US \$3.5 billion for damages and civil fines was filed against Novartis in 2015 by the FBI of the US government involving Exjade and Myfortic.<sup>15–17</sup>

Similarly, there are many misconceptions, inaccuracies, and omissions in the letter of Taher et al regarding the toxicity, efficacy, and cost of Exjade in comparison to deferoxamine and deferoxamine. Most of these issues have been extensively discussed in the past and reflect the commercial interference of pharmaceutical companies in academia, health authorities, medical literature, etc, all of which aim for the increase in sales of drugs.<sup>1–14,18–21</sup>

Taher et al omit to mention that the cause of fatal renal, hepatic, bone marrow, and hemorrhagic cases, as well as many other serious toxic side effects, including warnings about aluminum coadministration with deferasirox,

are included in the Exjade drug labels.<sup>18–21</sup> There are also misconceptions by Taher et al, since there is no difference in the use of chelating drug protocols for thalassemia major, intermedia, “non-transfusion-dependent thalassemia”, and other similar categories of patients with equivalent levels of iron load. In this context, the recent approval for the use of Exjade in iron loaded non-transfusion-dependent thalassemia patients does not mean that these patients have not been receiving effective treatment in the past 50 years nor that these patients cannot be continuously and effectively treated using deferoxamine and deferoxamine.<sup>22,23</sup> Furthermore, the long-term effective and safe use of deferoxamine and deferoxamine in iron loaded non-transfusion-dependent thalassemia patients outweighs any biased clinical trial results in a small number of deferasirox-treated patients controlled by Novartis.<sup>22,23</sup>

Major inaccuracies in the comments of Taher et al include the rate of mortality of 11.7% reported by the European Medicines Agency for deferasirox, whereas for deferoxamine and deferoxamine it is <0.1% in postmarketing surveillance including deaths in clinical trials.<sup>12,21</sup> Furthermore and most importantly, substantial and rapid reduction or complete removal of toxic iron deposits, as well as elevation of left ventricular ejection fraction is observed in deferoxamine- or deferoxamine/deferoxamine-treated thalassemia patients, whereas no such results are observed in deferasirox-treated patients, where such improvements are rare or even nonexistent.<sup>24,25</sup> The reduction or elimination of cardiac mortality since the introduction of deferoxamine in thalassemia patients worldwide has increased the survival of thalassemia patients to near normal life span levels, whereas the introduction of deferasirox is likely to reverse this improvement.<sup>13,26</sup>

Taher et al continue to mislead the medical community by reporting findings from Novartis-funded and -controlled clinical trials with deferasirox in thalassemia, which do not appear to be confirmed in clinical practice or by independent investigators.<sup>22,25,27</sup> For example, only ~10% of thalassemia patients are using deferasirox in Cyprus, whereas the majority are using deferoxamine either in combination with deferoxamine or as a monotherapy.<sup>13,26</sup>

The recent increase in the maximum dose of deferasirox from 30 mg/kg/d to 40 mg/kg/d and its suggested use in non-transfusion-dependent thalassemia patients with serum ferritin <300 ng/mL is a desperate attempt to improve the efficacy profile of deferasirox and its sales in comparison to deferoxamine and deferoxamine. However, these changes may further increase the toxicity risks, especially since earlier animal studies and clinical reports have shown fatal or serious renal and other toxicities.

In addition, there are misleading comments by Taher et al on the cost of deferasirox, which for example does not include any prophylactic renal and other clinical and biochemical tests for its toxicity, in comparison to deferoxamine and deferiprone. The high cost of deferasirox appears to affect patient treatment and safety, as well as government health budgets and the tax payers in general.<sup>11–14</sup> In particular, the high retail price makes deferasirox unavailable in developing countries where the vast majority of thalassemia patients live.<sup>11–14</sup>

Taher et al are public employees receiving undisclosed payments from Novartis for the promotion of Exjade, which may be contrary to the public and patients' interests.<sup>15–17</sup> In contrast, in my case as the inventor of the generic drug deferiprone and other investigational new drugs, these inventions are all part of academic research, which is widely described in the medical and other literature with no commercial involvement or receipt of any related income. This information was also disclosed to the journal during the submission of the paper.<sup>12</sup>

The author reports no conflicts of interest in the published paper entitled “Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes”, wherefore a statement/disclosure was submitted to the journal *Drug Des Devel Ther* before publication, indicating that “I have made the following discoveries: deferiprone (L1) and maltol iron<sup>28</sup> and also other discoveries, eg, deferoxamine (DF) suppositories.<sup>29</sup> I have also designed the combination of L1/DF<sup>30</sup> and the ICOC protocol.<sup>31</sup> I have also originally suggested the use of L1 in Friedreich ataxia, Parkinson's, and Alzheimer's diseases.<sup>32</sup> None of this work was supported by pharmaceutical or other commercial companies”. It should also be noted that the patent on the generic drug deferiprone expired over 10 years ago, and the author receives no income or consultancies or any other support by any commercial companies.

## Acknowledgments

The author is the director of the Postgraduate Research Institute of Science, Technology, Environment and Medicine, Limassol, Cyprus, which is a nonprofit, charitable organization.

## Disclosure

The author reports no conflicts of interest in this communication.

## References

- Davidoff F, DeAngelis CD, Drazen JM, et al. Sponsorship, authorship, and accountability. *JAMA*. 2001;286(10):1232–1234.
- Studdert DM, Mello MM, Brennan TA. Financial conflicts of interest in physicians' relationships with the pharmaceutical industry – self-regulation in the shadow of federal prosecution. *N Engl J Med*. 2004;351(18):1891–1900.
- Braillon A, Bewley S, Herxheimer A, et al. Marketing versus evidence-based medicine. *Lancet*. 2012;380(9839):340.
- Lochouart M. France launches new drug regulatory agency. *Lancet*. 2012;379(9832):2136.
- Yang Z, Fan D. How to solve the crisis behind BribeGate for Chinese doctors. *Lancet*. 2012;379(9812):e13–e15.
- Andersen M, Kragstrup J, Søndergaard J. How conducting a clinical trial affects physicians' guideline adherence and drug preferences. *JAMA*. 2006;295(23):2759–2764.
- Psaty BM, Rennie D. Clinical trial investigators and their prescribing patterns: another dimension to the relationship between physician investigators and the pharmaceutical industry. *JAMA*. 2006;295(23):2787–2790.
- Sacristán JA, Bolaños E, Hernández JM, Soto J, Galende I. Publication bias in health economic studies. *Pharmacoeconomics*. 1997;11(3):289–292.
- Holmes D. Skies darken over drug companies. *Lancet*. 2012;379(9829):1863–1864.
- Beran D, Capewell S, de Courten M. The International Diabetes Federation: losing its credibility by partnering with Nestlé? *Lancet*. 2012;380(9844):805.
- Kontoghiorghes CN, Andreou N, Constantinou K, Kontoghiorghes GJ. World health dilemmas: orphan and rare diseases, orphan drugs and orphan patients. *World J Methodol*. 2014;4(3):163–188.
- Kontoghiorghes CN, Kontoghiorghes GJ. Efficacy and safety of iron-chelation therapy with deferoxamine, deferiprone, and deferasirox for the treatment of iron-loaded patients with non-transfusion-dependent thalassemia syndromes. *Drug Des Devel Ther*. 2016;10:465–481.
- Kolnagou A, Kontoghiorghes CN, Kontoghiorghes GJ. Transition of thalassaemia and Friedreich ataxia from fatal to chronic diseases. *World J Methodol*. 2014;4(4):197–218.
- Kontoghiorghes CN, Kontoghiorghes GJ. New developments and controversies in iron metabolism and iron chelation therapy. *World J Methodol*. 2016;6(1):1–19.
- U.S. Attorney's Office [webpage on the Internet]. Manhattan U.S. Attorney Announces \$60 Million Civil Fraud Settlement with Accredo Health Group over Kickback Scheme Involving Prescription Drug; 2015. Available from: <https://www.fbi.gov/newyork/press-releases/2015/manhattan-u.s.-attorney-announces-60-million-civil-fraud-settlement-with-accredo-health-group-over-kickback-scheme-involving-prescription-drug>. Accessed August 4, 2016.
- LexisNexis Legal Newsroom Litigation [webpage on the Internet]. Another Specialty Pharmacy Settles Exjade False Claims Allegations for \$45 Million; 2015. Available from: <http://www.lexisnexis.com/legalnewsroom/litigation/b/litigation-blog/archive/2015/05/01/another-specialty-pharmacy-settles-exjade-false-claims-allegations-for-45-million.aspx>. Accessed August 4, 2016.
- REUTERS [webpage on the Internet]. U.S. seeks up to \$3.35 billion in Novartis kickback lawsuit; 2015. Available from: <http://www.reuters.com/article/2015/06/30/us-novartis-lawsuit-idUSKCN0-PA1ZK20150630>. Accessed August 4, 2016.
- Novartis Pharmaceutical Corporation [webpage on the Internet]. Exjade (deferasirox) tablets for oral suspension [prescribing information]. East Hanover, NJ: Novartis Pharmaceutical Corporation; 2011. Available from: [http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2010/021882s010lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021882s010lbl.pdf). Accessed August 4, 2016.
- Novartis Pharmaceuticals [webpage on the Internet]. EXJADE® (deferasirox) US Prescribing Information; 2015. Available from: <http://www.pharma.us.novartis.com/product/pi/pdf/exjade.pdf>. Accessed August 4, 2016.
- Kontoghiorghes GJ. Transparency and access to full information for the fatal or serious toxicity risks, low efficacy and high price of deferasirox, could increase the prospect of improved iron chelation therapy worldwide. *Hemoglobin*. 2008;32(6):608–615.

21. Kontoghiorghes GJ. A record number of fatalities in many categories of patients treated with deferasirox: loopholes in regulatory and marketing procedures undermine patient safety and misguide public funds? *Expert Opin Drug Saf.* 2013;12(5):605–609.
22. Cossu P, Toccafondi C, Vardeu F, et al. Iron overload and desferrioxamine chelation therapy in  $\beta$ -thalassemia intermedia. *Eur J Pediatr.* 1981;137(3):267–271.
23. Calvaruso G, Vitrano A, Di Maggio R, et al. Deferiprone versus deferoxamine in thalassemia intermedia: results from a 5-year long-term Italian multicenter randomized clinical trial. *Am J Hematol.* 2015;90(7):634–638.
24. Tanner MA, Galanello R, Dessi C, et al. Combined chelation therapy in thalassemia major for the treatment of severe myocardial siderosis with left ventricular dysfunction. *J Cardiovasc Magn Reson.* 2008;10:12.
25. Wood JC, Kang BP, Thompson A, et al. The effect of deferasirox on cardiac iron in thalassemia major: impact of total body iron stores. *Blood.* 2010;116(4):537–543.
26. Telfer PT, Warburton F, Christou S, et al. Improved survival in thalassemia major patients on switching from desferrioxamine to combined chelation therapy with desferrioxamine and deferiprone. *Haematologica.* 2009;94(12):1777–1778.
27. Al-Khabori M, Bhandari S, Al-Huneini M, Al-Farsi K, Panjwani V, Daar S. Side effects of deferasirox iron chelation in patients with beta thalassemia major or intermedia. *Oman Med J.* 2013;28(2):121–124.
28. Kontoghiorghes GJ. *The design of orally active iron chelators for the treatment of thalassaemia* [PhD thesis]. Colchester, UK: University of Essex; British Library Microfilm No D66194/86. 1982:1–243.
29. Kontoghiorghes G, Marcus RE, Huehns ER. Desferrioxamine suppositories. *The Lancet.* 1983;322(8347):454.
30. Kontoghiorghes GJ. Advances in oral iron chelation in man. *Int J Hematol.* 1992;55(1):27–38.
31. Kolnagou A, Kontoghiorghes GJ. Effective combination therapy of deferiprone and desferrioxamine for the rapid clearance of excess cardiac iron and the prevention of heart disease in thalassaemia: The protocol of the international committee on oral chelators. *Hemoglobin.* 2006;30(2):239–249.
32. Kontoghiorghes GJ, Neocleous K, Kolnagou A. Benefits and risks of deferiprone in iron overload in Thalassaemia and other conditions: comparison of epidemiological and therapeutic aspects with deferoxamine. *Drug Saf.* 2003;26(8):553–584.

Dove Medical Press encourages responsible, free and frank academic debate. The content of the Drug Design, Development and Therapy 'letters to the editor' section does not necessarily represent the views of Dove Medical Press, its officers, agents, employees, related entities or the Drug Design, Development and Therapy editors. While all reasonable steps have been taken to confirm the content of each letter, Dove Medical Press accepts no liability in respect of the content of any letter, nor is it responsible for the content and accuracy of any letter to the editor.

## Drug Design, Development and Therapy

### Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are the features of the journal, which

Submit your manuscript here: <http://www.dovepress.com/drug-design-development-and-therapy-journal>

has also been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Dovepress