PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting: a study protocol for a pilot and definitive randomised double-blind placebo-controlled trial (CannabisCINV)
AUTHORS	Mersiades, Antony ; Tognela, Annette; Haber, Paul; Stockler, Martin; Lintzeris, Nicholas; Simes, John; McGregor, Iain; Olver, Ian; Allsop, David; Gedye, Craig; Kirby, Adrienne; Morton, Rachael; Fox, Peter; Clarke, Stephen; Briscoe, Karen; Aghmesheh, Morteza; Wong, Nicole; Walsh, Anna; Hahn, Carmel; Grimison, Peter

VERSION 1 – REVIEW

REVIEWER	Carlo DeAngelis Sunnybrook Odette Cancer Centre, Canada
REVIEW RETURNED	17-Jan-2018

GENERAL COMMENTS	There is a need to design and conduct appropriate trials with medicinal cannabis extracts in oncology patients for various symptom management issues. I believe your trial protocol sets out a useful template for such trials. The dose titration strategy is of particular importance because the need for dose titration with this type of pharmaceutical intervention is key to ensuring appropriate efficacy comparisons are made. Page 6 lines 51-53 – It would be helpful to define “significant CINV” Page 7 and 8 – Under “Background Treatment” section – abbreviations for drug administration should be clarified, they are not necessarily universal. Please also clarify abbreviations in other parts of the manuscript if not already done. I believe for the most part most/all abbreviations are spelled out. One final check would be helpful. Page 9 – Definitive study – Please clarify that this will also be a secondary prophylaxis population (i.e. patient would have had to experienced “significant CINV” – to be defined, see above comment, from a previous cycle) For the definitive study you may want to consider what cycle the patient experienced “significant CINV” in as a stratifying factor in the randomization.

REVIEWER	Luici Celio Medical Oncology Unit 1, Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
REVIEW RETURNED	21-Jan-2018

GENERAL COMMENTS	This is an interesting research project on the management of CINV. However, some clarifications are needed about the methodology of

	the study protocol. Specific criticisms: Page 4 (line 17): the complete response defined as no vomiting and no use of rescue medications is a standard efficacy end point in clinical studies of CINV prophylaxis. Unfortunately, it does not include any direct assessment of the nausea control that is still an unmet need in the management of CINV. Since the traditional CR is not the end point used for planned studies, it is necessary to specify what is meant by CR in the abstract. Page 5 (lines 50-51): primary efficacy end point of the two planned studies is CR during the overall phase, defined as no nausea, no emesis, and no use of rescue medications. However, this end point is commonly referred to as total control of CINV. It is extremely important that the authors use appropriate terminology to avoid confusion in the reader. Page 6 (line 5): the definition of no significant nausea must be specified in the study protocol. Page 6 (lines 52-53): eligible patients must have had a significant CINV despite guideline consistent prophylaxis. The authors should better specify what is meant by “significant CINV”. Page 9 (line 38): since the nausea control is included in primary efficacy end point of the two planned studies, the tool used for nausea assessment (e.g., VAS or other) must be specified in the protocol. This is also an important point as “no significant nausea” is a secondary end point of the studies. Page 10 (lines 49-50): the authors state that “health outcomes will include the proportion of complete responders (i.e., participants with no emesis and no use of rescue medications)”. This is inconsistent with the primary efficacy end point of the definitive study. In addition, the use of traditional CR instead of the total control of CINV could have a more favorable impact on the results of the economic analysis.

REVIEWER	Linda A Parker Psychology and Neuroscience, University of Guelph, Guelph, ON N1G 2W1, Canada
REVIEW RETURNED	24-Jan-2018

GENERAL COMMENTS	While current anti-emetic therapies are quite effective in reducing vomiting, they are much less effective in treating chemotherapy-induced nausea. Therefore, there is a need for better treatments for nausea in particular. Considerable preclinical evidence indicates that cannabidiol (CBD) (e.g, Parker et al, 2000; Rock et al, 2012) and its acidic precursor CBD acid (CBDA) Bolognini et al, 2013) have potential for treating nausea (acute and anticipatory) and vomiting alone and in combination with THC both by injection (Rock et al, 2015; Rock & Parker 2015) and by oral administration (Rock et al, 2016). In fact, Rock & Parker (2015) found a synergistic effect of CBDA and ondansetron in the relief of nausea. In human clinical trials, as the authors review, Duran et al (2010) reported in a small pilot double-blind randomized trial that a THC/CBD cannabis extract (Sativex, GW Pharmaceuticals) had substantial efficacy in reducing emesis and delayed nausea produced by chemotherapy treatment. These findings suggest that it is definitely time to evaluate the potential of combined treatment of CBD and THC, especially for patients who fail to respond to the standard prophylactic anti-emetic regime. Antony Mersiades and colleagues present a protocol for an ongoing pilot and subsequent definitive randomized cross-over double-blind

	placebo-controlled trial to evaluate an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (along with guideline-consistent anti-emetics) in patients that are unresponsive to conventional anti-emetic treatment. For Cycle A, following an initial 24 hr administration of THC/CBD cannabis extract capsules (or placebo) to confirm tolerability, the patients will be administered either the active or placebo capsules on the day of treatment (1 hr before, immediately following and 4 hr later) and will be able to self-titrate (up to 12 capsules/day) their exposure on a subsequent 4 days. Then the patients will cross-over to Cycle B with the opposite treatment. Finally, in Cycle C they will receive the treatment that they preferred (THC/CBD or Placebo). The delay between cycles is not reported. The definitive study will follow the same design as Cycle A, but for cycle B, the patients will continue treatment with THC/CBD at their maximal tolerated dose from the previous cycle, with further scope to self-titrate according to symptoms. Data will be collected in self-report patient diaries and there will be daily assessment of patient on days 1-6 of each cycle to ensure that the treatments are taken, the patient is maintaining accurate records, to complete a checklist of cannabinoid-specific adverse events and to provide advice if needed. This critical study for improving the quality of life for chemotherapy patients is extremely well designed and will provide definitive evidence regarding the efficacy of THC/CBD treatment (in addition to standard anti-emetic treatment) in reducing nausea and vomiting in chemotherapy patients. It is timely and important for the world-wide health of cancer patients. References: Bolognini D, Rock EM, Cluny NL, Cascio MG, Limebeer CL, Duncan M, Stott CG, Javid FA, Parker LA, Pertwee RG. (2013) Cannabidiolic acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation. British Journal of Pharmacology, 168, 1456-1470 Duran M, Pérez E, Abanades S, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. British journal of clinical pharmacology 2010;70(5):656-63. Parker LA, Mechoulam R, Schlievert C, Abbott LA (2002) Cannabidiol, a non-psychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. NeuroReport, 13, 567-570. Rock, E.M., Connolly, C., Limebeer, C.L., Parker, L.A. (2016) Effect of combined oral doses of 9-tetrahydrocannabinol (THC and cannabidiolic acid (CBDA) on acute and anticipatory nausea in rat models. Psychopharmacology, 233: 3353-60 Rock EM, Limebeer CL, Parker LA (2015). Effect of combined doses of Δ9-tetrahydrocannabinol (THC) and cannabidiolic acid (CBDA) on acute and anticipatory nausea using rat models of conditioned

	gaping. Psychopharmacology, 232:445-54 . Rock EM, Parker LA (2015) Synergy between cannabidiol, cannabidiolic acid and Δ9-Tetrahydrocannabinol in the regulation of emesis in the Suncus murinus (house musk shrew). Behavioral Neuroscience, 129:368-70 Rock EM, Parker LA (2013) Effect of low doses of cannabidiolic acid and ondansetron on LiCl-induced conditioned gaping (a model of nausea) in rats. British Journal of Pharmacology, 169, 685-92.

VERSION 1 – AUTHOR RESPONSE

Reviewer(s) Reports:

Reviewer: 1
Reviewer Name: Carlo DeAngelis
Institution and Country: Sunnybrook Odette Cancer Centre, Canada
Please state any competing interests': Working with medicinal cannabis growers in Canada to develop and conduct clinical trails in cancer patients

Please leave your comments for the authors below

There is a need to design and conduct appropriate trials with medicinal cannabis extracts in oncology patients for various symptom management issues. I believe your trial protocol sets out a useful template for such trials. The dose titration strategy is of particular importance because the need for dose titration with this type of pharmaceutical intervention is key to ensuring appropriate efficacy comparisons are made.

Thank you very much for your considered appraisal of this trial protocol and role in the broader context of CINV management. We found your critique valuable and have attempted to address your specific comments.

Reviewer 1 comment	Response	Page
Page 6 lines 51-53 – It would be helpful to define "significant CINV"	**Added** significant CINV, defined as requiring ≥1 dose of rescue medication for vomiting or distress by nausea, and/or ≥ moderate nausea on a 5-point rating scale, at any time during the current chemotherapy regimen despite guideline consistent anti-emetics, (iii) no significant nausea, defined as degree of	5

(iii) no significant nausea	nausea <2 out of 10 using an 11-point rating scale,	4
Page 7 and 8 – Under "Background Treatment" section – abbreviations for drug administration should be clarified, they are not necessarily universal. Please also clarify abbreviations in other parts of the manuscript if not already done. I believe for the most part most/all abbreviations are spelled out. One final check would be helpful	**Previous wording** ♦ Lorazepam, eg 1mg PO bd prn ♦ Metoclopramide, eg 10mg PO tds prn ♦ Haloperidol, eg 0.5 – 1mg PO tds prn ♦ Prochlorperazine, eg 5 – 10mg PO tds prn, 25mg sup PR q8h prn ♦ Olanzapine, eg 5mg PO bd or 10mg PO mane for 3 days **New wording** ♦ Lorazepam, eg 1mg PO bd (twice a day) prn (when required) ♦ Metoclopramide, eg 10mg PO tds (three times a day) prn ♦ Haloperidol, eg 0.5 – 1mg PO tds prn ♦ Prochlorperazine, eg 5 – 10mg PO tds prn, 25mg sup PR (per rectum) q8h prn ♦ Olanzapine, eg 5mg PO bd or 10mg PO mane for 3 days	6
Page 9 – Definitive study – Please clarify that this will also be a secondary prophylaxis population (i.e. patient would have had to experienced "significant CINV" – to be defined, see above comment, from a previous cycle)	**Previous wording** The definitive randomised phase 3 study (N=250) will have a parallel group design, to reduce bias given the possibility of carry-over effect from cross-over in subsequent cycles, and to investigate longer-term efficacy over multiple chemotherapy cycles. **New wording** The definitive randomised phase 3 study (N=250) will assess the efficacy of the addition of TN-TC11M to guideline consistent anti-emetics as secondary prevention of CINV.	7-8
For the definitive study you may want to consider what cycle the patient experienced "significant CINV" in as a	Response: Thank you for the suggestion which is worthy of consideration. Given range of patient and treatment factors that can influence the experience of CINV a pragmatic approach has	NA

stratifying factor in the randomization.	been taken to limit the number of stratification factors.	

Page 6 lines 51-53 – It would be helpful to define "significant CINV"
Page 7 and 8 – Under "Background Treatment" section – abbreviations for drug administration should be clarified, they are not necessarily universal. Please also clarify abbreviations in other parts of the manuscript if not already done. I believe for the most part most/all abbreviations are spelled out. One final check would be helpful.

Page 9 – Definitive study – Please clarify that this will also be a secondary prophylaxis population (i.e. patient would have had to experienced "significant CINV" – to be defined, see above comment, from a previous cycle)

For the definitive study you may want to consider what cycle the patient experienced "significant CINV" in as a stratifying factor in the randomization.

Reviewer: 2
Reviewer Name: Luici Celio
Institution and Country: Medical Oncology Unit 1,
Department of Medical Oncology and Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
Please state any competing interests: None declared

Please leave your comments for the authors below

This is an interesting research project on the management of CINV. However, some clarifications are needed about the methodology of the study protocol.

Thank you very much for your considered appraisal of this trial protocol and role in the broader context of CINV management. We found your critique valuable and have attempted to address your specific concerns.

Reviewer 2 comment/criticism	Response	Page
Page 4 (line 17): the complete response defined as no vomiting and no use of rescue medications is a standard efficacy end point in clinical studies of CINV	This study will use the traditional 'complete response' (CR) end-point as the primary outcome measure. This is justified as it remains the most validated tool for the assessment of	

prophylaxis. Unfortunately, it does not include any direct assessment of the nausea control that is still an unmet need in the management of CINV. Since the traditional CR is not the end point used for planned studies, it is necessary to specify what is meant by CR in the abstract.	chemotherapy-induced nausea and vomiting. **Removed** – no nausea **New wording** The proportion of patients achieving a 'complete response' during the overall phase of treatment (0 - 120 hours), defined as no emesis and no use of rescue medications. We feel that an efficacy end-point that includes complete control of nausea, such as 'total control' may be difficult to achieve and could potentially jeopardise the further study of a class of drug that may be highly beneficial in a subset of the population. Nausea remains an important secondary endpoint used to address this issue. The study will separately report, the proportion of subjects experiencing significant nausea, defined as degree of nausea <2 out of 10 using an 11-point rating scale across the acute (0 – 24 hours), delayed (24 – 120 hours) and overall (0 – 120 hours) phases of cycles A, B and C is an important secondary end-point.	3
Page 10 (lines 49-50): the authors state that "health outcomes will include the proportion of complete responders (i.e., participants with no emesis and no use of rescue medications)". This is inconsistent with the primary efficacy end point of the definitive study. In addition, the use of traditional CR instead of the total control of CINV could have a more favorable impact on the results of the economic analysis.	We acknowledge the unmet need for nausea control a clinically important outcome that is often not represented as an endpoint in intervention trials CINV clinical trials. We have identified that fact that the primary end-point 'complete response' does not include the subject experience of nausea, and have listed it as a limitation of the study in the strengths and limitations of the study section.	9

	Removed Health related outcomes will include No nausea **Added** The definitive study will employ a health economic analysis which will use **Added** consistent with the primary endpoint). In addition we will conduct a sensitivity analysis to determine the incremental costs to achieve an outcome of no significant nausea, no emesis, and no use of rescue medications. **New wording** The definitive study will employ a health economic analysis which will use the proportion of patients with 'complete response' (i.e. participants with ~~no nausea,~~ no emesis and no use of rescue medications, consistent with the primary endpoint). In addition we will conduct a sensitivity analysis to determine the incremental costs to achieve an outcome of no significant nausea, no emesis, and no use of rescue medications. **Added** Limitations ♦ Primary outcome measure (complete response) does not include nausea assessment, to ensure comparability with other CINV trials	2
Page 5 (lines 50-51): primary efficacy end point of the two planned studies is CR during the overall phase, defined as no nausea, no emesis, and no use of rescue medications. However, this end point is	**Removed** – no nausea to leave **New wording**	3

commonly referred to as total control of CINV. It is extremely important that the authors use appropriate terminology to avoid confusion in the reader.	The proportion of patients achieving a 'complete response' during the overall phase of treatment (0 - 120 hours), defined as no emesis and no use of rescue medications.	
Page 6 (line 5): the definition of no significant nausea must be specified in the study protocol.	**Added** (iii) no significant nausea, defined as degree of nausea <2 out of 10 using an 11-point rating scale,	4
Page 6 (lines 52-53): eligible patients must have had a significant CINV despite guideline consistent prophylaxis. The authors should better specify what is meant by "significant CINV".	**Added** Experienced significant CINV, defined as requiring ≥1 dose of rescue medication for vomiting or distress by nausea, and/or ≥ moderate nausea on a 5-point rating scale, at any time during the current chemotherapy regimen despite guideline consistent anti-emetics,	5
Page 9 (line 38): since the nausea control is included in primary efficacy end point of the two planned studies, the tool used for nausea assessment (e.g., VAS or other) must be specified in the protocol. This is also an important point as "no significant nausea" is a secondary end point of the studies.	**Added** Nausea (past 24-hour period), recorded using an 11-point rating scale	8

Reviewer: 3
Reviewer Name: Linda A Parker
Institution and Country: Psychology and Neuroscience, University of Guelph, Guelph, ON N1G 2W1, Canada
Please state any competing interests: None

Please leave your comments for the authors below

Response: Thank you very much for your considered appraisal of this trial protocol and role in the broader context of CINV management. We are pleased you find it worthy of publication in it's current format.

Reviewer 3 comment	Response	Page
NA	**NA**	NA

While current anti-emetic therapies are quite effective in reducing vomiting, they are much less effective in treating chemotherapy-induced nausea. Therefore, there is a need for better treatments for nausea in particular. Considerable preclinical evidence indicates that cannabidiol (CBD) (e.g, Parker et al, 2000; Rock et al, 2012) and its acidic precursor CBD acid (CBDA) Bolognini et al, 2013) have potential for treating nausea (acute and anticipatory) and vomiting alone and in combination with THC both by injection (Rock et al, 2015; Rock & Parker 2015) and by oral administration (Rock et al, 2016). In fact, Rock & Parker (2015) found a synergistic effect of CBDA and ondansetron in the relief of nausea. In human clinical trials, as the authors review, Duran et al (2010) reported in a small pilot double-blind randomized trial that a THC/CBD cannabis extract (Sativex, GW Pharmaceuticals) had substantial efficacy in reducing emesis and delayed nausea produced by chemotherapy treatment. These findings suggest that it is definitely time to evaluate the potential of combined treatment of CBD and THC, especially for patients who fail to respond to the standard prophylactic anti-emetic regime.

Antony Mersiades and colleagues present a protocol for an ongoing pilot and subsequent definitive randomized cross-over double-blind placebo-controlled trial to evaluate an oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting (along with guideline-consistent anti-emetics) in patients that are unresponsive to conventional anti-emetic treatment. For Cycle A, following an initial 24 hr administration of THC/CBD cannabis extract capsules (or placebo) to confirm tolerability, the patients will be administered either the active or placebo capsules on the day of treatment (1 hr before, immediately following and 4 hr later) and will be able to self-titrate (up to 12 capsules/day) their exposure on a subsequent 4 days. Then the patients will cross-over to Cycle B with the opposite treatment. Finally, in Cycle C they will receive the treatment that they preferred (THC/CBD or Placebo). The delay between cycles is not reported.

The definitive study will follow the same design as Cycle A, but for cycle B, the patients will continue treatment with THC/CBD at their maximal tolerated dose from the previous cycle, with further scope to self-titrate according to symptoms.

Data will be collected in self-report patient diaries and there will be daily assessment of patient on days 1-6 of each cycle to ensure that the treatments are taken, the patient is maintaining accurate records, to complete a checklist of cannabinoid-specific adverse events and to provide advice if needed.

This critical study for improving the quality of life for chemotherapy patients is extremely well designed and will provide definitive evidence regarding the efficacy of THC/CBD treatment (in addition to standard anti-emetic treatment) in reducing nausea and vomiting in chemotherapy patients. It is timely and important for the world-wide health of cancer patients.

References:

Bolognini D, Rock EM, Cluny NL, Cascio MG, Limebeer CL, Duncan M, Stott CG, Javid FA, Parker LA, Pertwee RG. (2013) Cannabidiolic acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation. British Journal of Pharmacology, 168, 1456-1470

Duran M, Pérez E, Abanades S, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. British journal of clinical pharmacology 2010;70(5):656-63.

Parker LA, Mechoulam R, Schlievert C, Abbott LA (2002) Cannabidiol, a non-psychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. NeuroReport, 13, 567-570.

Rock, E.M., Connolly, C., Limebeer, C.L., Parker, L.A. (2016) Effect of combined oral doses of 9-tetrahydrocannabinol (THC and cannabidiolic acid (CBDA) on acute and anticipatory nausea in rat models. Psychopharmacology, 233: 3353-60

Rock EM, Limebeer CL, Parker LA (2015). Effect of combined doses of Δ9-tetrahydrocannabinol (THC) and cannabidiolic acid (CBDA) on acute and anticipatory nausea using rat models of conditioned gaping. Psychopharmacology, 232:445-54
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Rock EM, Parker LA (2015) Synergy between cannabidiol, cannabidiolic acid and Δ9-Tetrahydrocannabinol in the regulation of emesis in the Suncus murinus (house musk shrew). Behavioral Neuroscience, 129:368-70

Rock EM, Parker LA (2013) Effect of low doses of cannabidiolic acid and ondansetron on LiCl-induced conditioned gaping (a model of nausea) in rats. British Journal of Pharmacology, 169, 685-92.

VERSION 2 – REVIEW

REVIEWER	Luigi Celio MD, Senior Medical Oncologist Fondazione IRCCS Istituto Nazionale dei Tumori - Milan, Italy
REVIEW RETURNED	26-Apr-2018

GENERAL COMMENTS	No further comments.

REVIEWER	Carlo DeAngelis Sunnybrook Odette Cancer Centre, Canada
REVIEW RETURNED	02-May-2018

GENERAL COMMENTS	Thank you for addressing the reviewer comments in a thorough and thoughtful manner.