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Climate footprint of industry-sponsored clinical research: an analysis of a phase-1 randomised clinical study and discussion of opportunities to reduce its impact

Jason Keith LaRoche ,[1,2] Rodrigo Alvarenga,[3] Michael Collins,[4] Thomas Costelloe,[5] Wouter De Soete,[6] Jeremy Faludi,[2] Kristel Rens[6]

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[1]Janssen Clinical Innovation, Janssen Research and Development LLC, Titusville, New Jersey, USA
[2]Industrial Design Engineering, Delft University of Technology, Delft, The Netherlands
[3]Environmental Resources Management, Ghent, Belgium
[4]Product Sustainability, Environmental Resources Management, Edinburgh, UK
[5]Environmental Resources Management, Bletchley, UK
[6]Janssen Pharmaceutica NV, Beerse, Belgium

Correspondence to
Dr Jason Keith LaRoche; jlaroche@its.jnj.com

ABSTRACT

Objective This study aims to calculate the global warming potential, in carbon dioxide (CO2) equivalent emissions, from all in-scope activities involved in a phase-1 clinical study.

Design Retrospective analysis.

Data source Internal data held by Janssen Pharmaceuticals.

Studies included Janssen-sponsored TMC114FD1HTX1002 study conducted between 2019 and 2021.

Main outcome Measure CO_2 equivalents (CO_2e) for in-scope clinical trial activities calculated according to intergovernmental panel on climate change 2021 impact assessment methodology.

Results The CO_2e emissions generated by the trial were 17.65 tonnes. This is equivalent to the emissions generated by driving an average petrol-fueled family car 71 004 km or roughly 1.8 times around the circumference of the Earth. Commuting to the clinical site by the study participants generated the most emissions (5419 kg, 31% of overall emissions), followed by trial site utilities (2725 kg, 16% of overall emissions) and site staff travel (2560 kg, 15% of overall emissions). In total, the movement of people (participant travel, site staff travel and trial site staff travel) accounted for 8914 kg or 51% of overall trial emissions.

Conclusions Decentralised trial models which seek to bring clinical trial operations closer to the participant offer opportunities to reduce participant travel. The electrification of sponsor vehicle fleets and society's transition towards electric vehicles may result in further reductions.

Trial registration number NCT04208061.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Study limitations are associated largely with the available data, and the data gaps filled by proxy values or assumptions.
⇒ Efforts were made to establish more representative proxy data and assumptions for the modelled system, but further primary data collection would be valuable in improving the robustness and accuracy of the study.
⇒ Despite the limitations, overall, the assessment is a reasonable estimate of the impact and key drivers of impact for this phase I clinical trial.
⇒ While the results of this study relate to the specific clinical trial assessed, if differences are acknowledged then it may be extrapolated in general terms to the design and operation of other clinical trials providing an indication of the environmental impact of broader phase-1 clinical research.

INTRODUCTION

A phase-1 study represents the first testing of a new drug in humans primarily to assess safety. A drug is given to a small group of healthy volunteers who are then closely monitored. If the safety profile of the drug is favourable then it may advance to phase-2 where a small group of volunteers with the targeted disease are given the drug to further assess safety, understand how the drug is metabolised and begin to assess efficacy. If the safety and efficacy profile continue to prove favourable, then a drug may advance to phase-3 where a larger population of volunteers with the targeted disease are exposed to the drug for continued evaluation of safety and efficacy. Phase-3 studies provide the safety and efficacy data required to obtain regulatory approval for the commercial marketing of a new drug.

Life cycle assessment (LCA) is a standardised method[1] for assessing the potential environmental impacts of product systems, taking into consideration all processes related to the product or service life cycle and all relevant environmental impacts.[2] Many companies, business associations and policymakers use this method as a decision-support tool, providing a quantitative evaluation of environmental sustainability. While LCA methodology allows for the assessment of a broad range of environmental impacts such as land use, water acidification and toxicity,

this LCA focused only on measuring the climate impact of the clinical trial system.

This publication uses an LCA to measure the greenhouse gas (GHG) emissions of a phase-1 clinical study sponsored by Janssen Pharmaceuticals. The LCA was inclusive of clinical site utilities and other gaps observed in earlier research. It seeks to shed light on the GHG emissions of clinical research and discuss opportunities to reduce those emissions. The goals of this LCA were threefold: to benchmark the GHG emissions of a phase-1 pharmaceutical trial, identify primary drivers affecting GHG emissions, and inform clinical trial sponsors and those involved in designing clinical trials of potential opportunities to mitigate the impacts of these hotspots.

METHODS

An LCA was performed on a Janssen (sponsor) phase-1 clinical study under ClinicalTrials.gov registry identifier TMC114FD1HTX1002, which was conducted in the years 2019–2021. The clinical study compared separate oral tablet formulations of the marketed drugs ritonavir and cobicistat against a new fixed-dose combination tablet containing both drugs. The study involved a single clinical trial site located in Antwerp, Belgium. As a phase-1 clinical study, healthy volunteers were recruited from the local community. 140 subjects were screened for eligibility to participate in the trial, with a total of 39 selected: 28 randomised into the trial and an additional 11 selected to serve as reserve subjects. A mix of in-patient care and at-home administration of drug products was involved in the study.

Participant and public involvement

While participants and the public were involved in the TMC114FD1HTX1002 clinical study (ClinicalTrials.gov: NCT04208061), the LCA was performed as an independent postmortem analysis after the clinical study was completed. As a postmortem analysis, we leveraged clinical trial documentation and interviews with the sponsor trial staff, and study site staff. None of the participating trial subjects were involved specifically in the LCA analysis nor was any personal identifying information from the trial subjects collected or shared.

The underlying clinical study was performed in accordance with the Declaration of Helsinki and Guidelines for Good Pharmacoepidemiology Practice. All participating investigators were required to obtain full governing board approval for conducting non-interventional research involving humans with a limited dataset.

In the underlying clinical study, the 140 subjects screened visited the clinical site once. Subjects randomised into the study visited the site a subsequent six times. The reserve subjects only visited the site one time spending one overnight stay in in-patient care before being discharged. Randomised subjects initially underwent 1 week, or six nights, of in-patient care where they remained at the clinic to be closely monitored and provided a specific diet to control for drug–food interactions. After the six nights of in-patient care, they were allowed to return home where they continued to take their drug remotely over a period of 3 weeks. During the at-home portion, subjects made five visits to the site for health and safety exams. Online supplemental figure A further illustrates the involvement of different subject groups in the clinical study.

LCA methodology

The LCA was conducted under a dynamic and iterative approach in accordance with ISO 14040/44 standards, and peer reviewed by a third party. The system boundary of the LCA is summarised in table 1 and visually represented in online supplemental figure B.

Goal and scope of the study

Data sources

According to the definitions of the Life Cycle initiative,[3] the foreground system consists of processes/activities which are under the control of the decision-maker for which an LCA is carried out. The background system consists of processes on which no or, at best indirect, influence can be exercised by the decision-maker. For this LCA, the foreground system is the activities/processes presented in online supplemental figure B. The background system is all supporting activities/processes, including electricity production, energy/heat production, transport operations and incineration processes.

For foreground data, certain key parameters (eg, distances, number of visits of participants) are provided as primary data by the case study. Foreground data such as distance and mode of transport for participants, site staff and sponsor staff was based on administered surveys. Participant responses were anonymised by site staff with only distance and mode of transport provided for analysis. Food impacts, under the participant accommodation category, were based on documented menus served to participants with secondary data and assumed ingredient masses used to assess the impact of individual food products. Food served on-site was included as it was specifically prepared foods to test drug-food interactions, and therefore, an item controlled by the decision-maker.

The drug products used in the trial were Pradaxa (150 mg), ritonavir (100 mg), darunavir (800 mg) and darunavir/cobicistat (800 mg/150 mg). Data concerning the number of tablets of each drug used during the trial were provided by Janssen. The location of formulation for each drug was provided by Janssen and is presented table 2. As no analogous data for active pharmaceutical ingredient (API) production were provided, this was assumed to take place at the same location.

No LCA data or LCA impact values were available for the production of the drug products. Data sourced from the Association of British Pharmaceutical Industry (ABPI) sustainability tool[4] have been used to estimate the impacts associated with the production of API. A range from low (600 kg carbon dioxide equivalents (CO_2e/kg)), medium (1500 kg CO_2e/kg) and high (7000 kg CO_2e/kg)

Table 1 System boundary summary

Category	Study activity
Included activities	Patient transport to and from the clinical site based on distance and mode of transport as reported by participating subjects
	Drug product manufacturing from production of the active pharmacological ingredient through the final packaging and labelling of the drug product for use in the study. This included transportation of material between intermediate stages of production.
	Distribution of the study drug from packaging (Beerse, BE) to delivery to the clinical site (Antwerp, BE) via truck
	Clinical site emissions including utilities, consumables (eg, exam gloves and other materials), travel of study-related site staff to and from their homes and the clinical site and equipment such as computers and instruments involved in study conduct
	Consumables involved in the collection of laboratory samples (eg, patient blood panels) and the transport and processing of those samples at a central laboratory
	Trial sponsor activities including ► On-site monitoring visits. ► Utility consumption of all supporting study personnel whether they worked from the office or from home. ► Equipment such as laptops utilised by sponsor personnel. ► Travel to and from home to the office.
	External meetings include a local independent review board (IRB) meeting to review and approve the study design. All IRB members were local to the meeting location in Antwerp, BE
Excluded activities	Emissions occurring at the patient's home during at-home administration of the drug product were excluded as participation in the study had no influence on at-home emissions
	Land use associated with Janssen employees, trial site investigators and patients, due to their expected immateriality
	Capital goods and infrastructure

emission factors have been used for cobicistat, Pradaxa, ritonavir and darunavir. Medium values were used for the baseline calculation, while the low/high ends of the range were considered in a sensitivity analysis.

An LCI inventory for API production has been reverse-engineered using the above estimated emission factors. It has been assumed that the impacts of API production are driven by the production of solvent, and its subsequent incineration (assumed to be represented by 1 kg of acetone and 1 kg of solvent waste treatment by hazardous incineration).

The impacts of drug formulation have been estimated using data sourced from the ABPI sustainability tool, that is, utilities consumptions of 14.31 kWh of electricity and 14.40 kWh of heating (natural gas) per kg of drug product formulated. Each tablet has been assumed to have an individual mass of 1 g.

Table 2 Production location of drug product used in the study

Drug product	Production location
Pradaxa (150 mg)	Boehringer Ingelheim, Berkshire, UK
Ritonavir (100 mg)	Abbott Lab, Berkshire, UK
Darunavir (800 mg)	Janssen, Latina, Italy
Darunavir/cobicistat (800 mg/150 mg)	Janssen, Gurabo, Puerto Rico

Other sources of foreground data were based on estimations or calculations, such as electricity use during the participant's treatment. These were estimated by allocating percentages of monthly utility charges to the clinical pharmacology unit responsible for study conduct.

Background data characterising activities in the background system were drawn from the Ecoinvent Database V.3.8[5] and used as alternative data to represent foreground processes where more reliable primary data (or good estimations) are not available.

All data used in our analysis are publicly available through DRYAD.[6]

Allocation procedures

Metered consumption data for utilities at the trial site were not available. As a result, trial site data were obtained by allocating a proportion of a yearly utilities invoice for the local integrated hospital. Emissions from energy production were based on the energy mix of Belgium. Specific trial data were then allocated, based on the number of trial subjects in this study compared with the total number of trial participants supported over the year.

For sponsor utilities (trial management), estimation via allocation was not required, as the data were drawn from a bottom-up secondary source of data based on the numbers of full-time equivalents working on the trial. The sponsor study team was based in Belgium. The number of hours worked by sponsor staff in sponsor facilities was

provided by Janssen and converted into person-years (assuming 2080 working hours per person-year). The total amount of person-years worked by sponsor staff at sponsor facilities during the trial was 2.117 person-years. Assuming that there are 236 commutes per person-year (52 weekends and 25 days of annual leave), this results in a total of 499.7 commutes by sponsor staff. Secondary data were sourced indicating that mean distance travelled by European workers is 28.56 km.[7] Mode of travel was based on the transportation mix for a commute in Belgium,[8] which was characterised using emission factors sourced from Ecoinvent.

Shared equipment and other healthcare infrastructure were excluded, as it was considered to have a lifespan significantly longer than the clinical trial period. In those cases where materials were used exclusively for the clinical trial, no allocation was needed (ie, the material was allocated entirely to the clinical trial).

Nearly all the consumables, testing kits and drugs used in the trial are treated as single use and, therefore, no recycling or re-use was considered. The exception was the sample courier packaging used for ambient sample transport, which is assumed to be re-used across multiple trials, where a cut-off method has been applied to account for the exclusion of end-of-life impacts. For consumables, we assumed incineration as the method of waste disposal.

Life cycle impact assessment method

The environmental impact of the study, expressed by the global warming potential, was calculated according to the intergovernmental panel on climate change 100 years method based in kilograms of CO_2e.[9]

RESULTS

The total GHG emissions for the study were estimated at 17 648 kg CO_2e. This is equivalent to driving a car for 71 004 km or roughly 1.8 times around the circumference of the Earth (based on typical petrol fueled passenger car by the US Environmental Protection Agency).[10] The results of the LCA of the phase I study are listed in table 3 by absolute kilograms of CO_2 equivalents and by percentage contribution to the total emissions.

The greatest contributor to overall GHG emissions was travel (of participants, study and sponsor staff) accounting for 51% (8914 kg CO_2e) of total emissions. The second largest contributor was study site facilities which included in-patient care during the first week of the study and the contribution of utilities associated with the site facilities during the conduct of the trial. The lowest contributors to GHG emissions were related to the transport and processing of laboratory samples (807 kg CO_2e; 5% of total). Online supplemental figure C provides a graphical representation of the primary contributors to the overall GHG emissions for the study.

Table 3 Environmental Impact of phase-1 study TMC114FD1HTX1002

Category	Clinical trial activity	Kg CO2e	% of total
Travel related	Participant travel	5419	31
	Trial site staff commuting	909	5
	Sponsor staff commuting	2560	15
	External meetings	26	0
Total		8914	50
Drug related	Drug product	890	5
Total		890	5
Study related	Trial site utilities	2725	15
	Participant accommodation	2068	12
	Sponsor facility utilities	1319	7
	Testing kits and consumables	925	5
	Laboratory sample transport and processing	807	5
Total		7844	44
Study total		17 648	100

CO2e, carbon dioxide equivalents.

DISCUSSION

Historically, LCAs of pharmaceuticals have been process or product-driven, either focusing on part of the pharmaceutical supply chain[11–13] or assessing the footprint of a product.[14] However, LCA boundaries have gradually expanded, and a new focus has emerged. This new area recognises that pharmaceuticals as a product are just one element of a larger care pathway featuring healthcare provider visits, hospitalisation and/or outpatient care.[15–17] A limitation of this research is that it has focused on typical care pathways in a commercial setting after a drug has received regulatory approval and has often neglected the environmental impact of clinical research required to bring those drugs to market.

As national healthcare systems such as those of Denmark and the UK establish net-zero ambitions,[18] their role in clinical research and the impact it may have on their efforts cannot be overlooked. The few publications that assess the climate impact of clinical research[19] are of limited scope and/or include assumptions that do not align with our findings or the findings of other published research. They fall into two categories: those that underestimate the impact of patient travel or those that neglect the impact of GHG emissions at clinical trial sites.

For the former category, Lyle *et al*[20] assumed that participant travel to and from the site was like that of a typical general practice in the UK, with travel of 2.4 km for primary care and 17.4 km for secondary care visits. This runs counter to other research where Borno *et al*[21] performed a retrospective analysis of the travel burden faced by 1600 US-based patients with cancer who participated in clinical trials and found the median roundtrip

distance to be 83.04 km. A second industry-led assessment of 600 participants,[22] reported the median roundtrip travel exceeding 80 km, magnitudes greater than the assumptions of Lyle *et al*.[20] In our own research, we found that on average patients were travelling 78.5 km roundtrip. This led to patient travel being the largest contributor, 31%, of overall GHG emissions in our analysis.

The second category of publications[23 24] exclude GHG emissions at the clinical sites despite other research[16] and our own findings that site utilities contributed to 15% of overall trial emissions making them a substantial source of emissions.

Overall, we found that one phase-1 trial resulted in 17 648 kg CO2e. Our research indicated that the largest drive was patient travel with a 31% contribution to trial emissions. Other drivers with a greater than 10% contribution were sponsor and trial site utilities (22% combined), sponsor staff commuting (15%) and patient accommodation (12%). Opportunities exist to reduce these hotspots as we will further discuss.

Opportunities for GHG reductions

Participant travel

The phase-1 study involved healthy volunteers recruited locally from the municipality of Antwerp, Belgium. As this was a retrospective study analysis, we were unable to survey participants regarding the mode of transport they used. Anecdotally, site personnel recalled participants only travelling by automobile. Given the distance of travel and this anecdotal evidence, we assumed only automobile transport was used. The similarity in reported distances in published research[21 22] indicates that the scale and climate impact of participant journey as measured in our phase-1 study is translatable to clinical studies conducted in other regions of Europe and the USA. Given its role as a major hotspot for GHG emissions in clinical research, this makes its reduction a tantalising target for reducing overall clinical trial emissions.

Seidler *et al*[25] found that clinical trials in the USA have traditionally been clustered in large urban areas with healthcare/social service facilities. This forces those participants in rural settings to travel further to gain access to clinical research.[26] Decentralised clinical trial (DCT) models offer the promise of reducing participant travel by bringing clinical trial activities closer to the participant's home. Telemedicine is the best option, as it allows participants and trial staff to meet virtually without any travel by either group. For lab sample collection and physical exams, local home healthcare professionals can perform home visits, reducing the travel of the clinical staff. Local laboratory services more proximal to the participant's home will reduce patient travel to and from the point of collection. Alternatively, deployment of local points of care, such as retail pharmacies or local clinics, can reduce the distance of travel required by the participant. The Walmart retail chain recently announced a strategy of using their retail clinics for clinical research, and 90% of the US population lives within 16 km of one of their US retail stores.[27 28]

To deliver on this promise, DCT models must be deployed wisely. While a travelling home healthcare professional may alleviate the need for a participant to visit the clinical trial site, if that home healthcare professional travels a further distance to reach the participant's home and/or uses a form of transportation with higher GHG emissions then we may see a net increase in GHG emissions.

Careful consideration must also be given to the deployment of technology that enables DCT models. Telemedicine technology has the potential to eliminate participant travel for select meetings with clinical site staff. Purohit *et al*[29] found that telemedicine consistently demonstrated reductions in GHG emissions. The savings ranged from 0.70 to 372 kg CO_2e per consultation depending on the distance of travel avoided. Ong *et al*[30] estimated that a teleconference using desktop computers would consume 351W of energy per hour. This is similar to the emissions from driving a typical petrol-fueled family car less than half of a mile.[10] In our study, the mean participant trip generated 17.03 kg of CO_2e: 85 times that generated by teleconferencing technology. This calculation assumes that the telemedicine equipment is being used for other purposes for at least 5 hours per day. In clinical trials, not every participating participant has a device for telemedicine, and often trial sponsors will need to provision a device. The emissions from the manufacture of a provisioned device would need to be added to the total. For example, when telemedicine is used by Janssen, a smartphone is provided to the patient. Manufacture of this device generates 57 kg of CO2e,[31] the equivalent of 3.4 patient visits to the clinical site (online supplemental figure D). Therefore, at least four visits would need to be avoided in order to offset the provision of a smartphone. Alternatively, when smartphones are provisioned to participants, establishing processes for collecting and refurbishing the devices at the end of the trial so they can be used again in another trial can spread the imbedded carbon from manufacture across multiple clinical trials and reducing the burden on any single trial.

A second challenge of DCT models is their benefits are not absolute. First, capabilities such as telemedicine are not suitable for cardiology and oncology trials where the ability of the study physician to physically examine the participant is important. Second, not every participant will be willing to adopt the DCT capabilities available to them. Some participants may prefer to travel to their clinical site for their visits because they appreciate a more natural and direct face-to-face engagement with the site's staff. Others may not feel comfortable having a home health professional visiting their home, while some participants may not feel comfortable using the digital technology that supports telemedicine, electronic clinical outcomes assessments and electronic diaries.

Deployment of local laboratory services and alternative points of care should seek to leverage infrastructure that

is already in place. Piggybacking on existing capital infrastructure in this manner can reduce the climate burden attributed to clinical studies which leverage it, while increasing utilisation of the infrastructure and potentially extending its profitable life. If DCT capabilities leverage existing local staff, then the additional environmental impacts of employee travel between home and work should remain minimal. However, if new infrastructure must be created, such as the construction of new local clinics to reach rural populations, any carbon savings from the DCT model will be lost.

Sponsor and trial site utilities

The heating, cooling and lighting of hospitals and clinics is a major driver of GHG emissions in healthcare[32] and the results of the LCA echoed this with site utilities driving 16% of the overall study emissions. A challenge in the LCA analysis was that we had no direct measure of the utility consumption of the study. Since the clinical site only conducts phase-1 studies of similar complexity, we assumed that participant visits to the clinical site are the primary driver of utility consumption for the study. We took the total number of participant visits under the study as a proportion of study visits across all studies in the same period as the method of allocating a portion of overall site utilities to the study. It should be cautioned that for clinical sites conducting a more diverse array of studies, particularly where site visits vary in complexity, a more reliable method of allocation is needed. Consider a vaccine study where participants undergo only routine safety follow-ups after administration of a vaccine and compare it to an oncology study that may involve in-patient infusion of drug product, complex imaging such as MRI and frequent blood sample analysis. The additional activities involved in each visit of the oncology study will lead to much higher consumption of utilities compared with the vaccine study. Allocation based on participant visits alone would be unsuitable when such diversity in trials exists. In our case, because all phase-1 studies supported by the clinical site were of similar complexity, we feel that the selected allocation approach is valid.

Utilities for sponsor offices contributed an additional 8% of overall study emissions. As the study conduct overlapped the occurrence of the COVID-19 pandemic, sponsor employees worked from home during a portion of the study conduct. An assessment of time reporting data allowed us to account for the total number of days employees worked from home versus the office. Secondary data were used to estimate the GHG emissions generated by employees working from home. A shift towards sourcing electricity from renewables poses the greatest opportunity to reduce the contributions of this category. Janssen has committed to shifting to 100% renewable electricity by 2025,[33] so the emissions from sponsor site utilities should rapidly decrease as this target date approaches.

As the world exits the pandemic, a growing number of employees are continuing to work from home for a greater portion of the work week.[34] Janssen itself has established a new policy requiring employees to only work from the office 3 days per week. The impact of this move creates an interesting dilemma, as Janssen facilities transition towards 100% renewable energy by 2025, many employee homes may continue to rely on local energy mixes that feature fossil fuels. While employees may turn off lights and adjust their home thermostat while away at the office, at-home work may keep lights and thermostat settings unchanged. This could result in work-from-home arrangements offsetting the efforts of Janssen to reduce the climate footprint of its workplace.

Sponsor staff commuting

Local sponsor staff are provided with a company car under existing employment contracts. The sponsor is exploring transitioning company cars from petrol to electric which should lead to a reduction in emissions, as well as encouraging staff to use public transportation or bicycle to work. Flexible work options that allow employees to work from home will also help to reduce the GHG emissions from sponsor staff commuting. Rietmann *et al*[35] attempted to forecast the trajectory of electric passenger vehicle sales across 26 countries along with its impact on worldwide CO_2 emissions. It was estimated that for Belgium, where the sponsor study team was based, a 54.2% reduction in CO_2 emissions from passenger vehicles would occur by 2035 compared with a 2018 baseline.

Participant accommodation

As in-participant care and associated overnight accommodation do not universally occur in phase-1 clinical studies, the GHG emissions of the associated activities were intentionally segregated into their own module. Electricity consumptions (eg, washing, television) were included in 'top-down' site utilities. Material impacts of linen, beds, chairs, etc were assumed to be negligible as re-used multiple times and were part of infrastructure. Where a hospital bed might have a lifespan of several years, when amortised to a single week's use the environmental impact was negligible. In the participant accommodation module, the largest contribution to the total impact (66%) is made by the participant lunches provided. Dinners and breakfasts make a smaller contribution, approximately 16% each. These impacts are driven by the consumption of beef and sausage meat, with beef meatballs contributing 75% of the total participant accommodation impact (and 95% of the impact per lunch). Sausage meat, used in both breakfast and dinner, contributes 13% of the total participant accommodation impact (online supplemental figure E). The enviornmental impacts of the different meal components are captured in table 4.

Drug product

While drug product contributed less than 10% of the overall study emissions in the study, we recognise data limitations and anticipate a larger contribution in larger multisite studies. The drug product module considers

Table 4 Environmental Impact of patient meals during in-patient stay

Activity	Subactivity	Kg CO_2e	% of total
Breakfast	Meat component	125	6
	Non-meat component	196	9
Lunch	Meat component	1301	63
	Non-meat component	68	3
Dinner	Meat component	134	6
	Non-meat component	204	10
Snack	Non-meat component	40	2
Total		2068	100%

CO2e, carbon dioxide equivalents.

API production, drug manufacture, packing and distribution to site, with 97% of the impact of this module is associated with API production. It is important to highlight the uncertainty associated with these results, as primary data for API were not available for the four drugs. A proxy value, based on the ABPI tool and assumptions, was used in order account for this stage in the LCA study in a consistent way. The impacts associated with drug product wastage, and all packaging, are shown to make a negligible contribution to the drug product impact (<1%). A sensitivity analysis was undertaken to determine how the results would change if the upper and lower ends of the range for API were used. The results are summarised in table 5.

In the base case, the drug product module contributes only 1% of the climate change impact. When the high end of the range is used, the contribution of the drug product becomes closer to that of other modules, such as samples (807 kg CO_2e), and comprises 5% of the overall impact. We assumed a worst-case scenario and used the high-range value in our analysis.

The emissions from the manufacture and packaging of drug product were relatively small in the study, contributing an estimated 5% of overall study emissions. It is expected that the contributions of drug product will be larger in a multisite study, and particularly in large global studies with long trial durations.

Table 5 Sensitivity analysis on GHG emissions from drug product manufacture

Sensitivity parameter	Total trial impact (kg CO_2e)	Drug product impact (kg CO_2e)	% of total
Low range	16 838	80	0.48
Medium range (base case)	16 952	194	1.15
High range	17 648	890	5.04

CO2e, carbon dioxide equivalents; GHG, greenhouse gas.

The study involved just a single clinical site with the forecasted recruitment and dosing of participants occurring within the shelf life of the drug product. This allowed the sponsor to package just enough drug to dose the 28 randomised subjects with minimal overage for replacement of lost/damaged drug during the at-home administration phase of the study. This minimised the quantity of involved study drug and its associated emissions. In multisite studies, sponsors must account for variability in participant enrollment across different sites. This requires the addition of local safety stock to accommodate enrolment that exceeds what was forecasted at a given site, increasing the quantity of drug product manufactured and packaged to support the study. Kachwala *et al*[36] estimate a 50% waste rate for drug product in clinical research, largely driven by larger and more complex clinical trials. Assuming a 50% waste rate on additional local safety stock, we would see the relative contribution of drug product increase to 1335 kg CO_2e with a relative contribution of 7%.

If study recruitment and dosing timelines exceed drug product shelf life, then this will also result in increases in drug product consumption. If fewer participants enrol than forecasted during the shelf life of the drug product, then not all packaged drug will be consumed and the remaining drug product will expire on the shelf. This expired drug will be wasted and will need to be replaced via the manufacture and packaging of new batches of drug product, increasing the overall consumption of drug product during the study.

CONCLUSION

In our analysis of the climate footprint of a phase-1 study, the transport of people was the greatest contributor of GHG emissions (51%), with participants (31%), employees (15%) and clinical staff (5%) all needing to travel from home to the clinical site or workplace.

The scale of transport's contribution makes it a prime target for reducing the GHG emissions for clinical trials. DCT models present an opportunity to reduce participant travel but they need to be deployed wisely to ensure that they do not generate more GHG emissions than they offset. Transition towards electric vehicles and use of public transportation can further reduce the emissions from the transport of people.

GHG emissions from the heating, cooling and lighting of the clinical trial site (16%) combined with utilities for the sponsor office space (8%) contributed to 24% of the overall study emissions. Transitioning towards renewable energy sources has the potential to reduce these emissions hotspots.

Participant accommodation, consumables and laboratory sample transport and processing contributed to the remaining 25% of the overall study emissions. While opportunities exist to make reductions in these areas, they may be the most difficult to change because they are the clinically relevant parts of the trials, with technologies

and procedures that could change patient outcomes. Therefore, the overall focus should be on reducing emissions from the transport of people and site and sponsor utilities.

Contributors JKL, WDS and KR conceived of and presented the idea. All authors (JKL, RA, TC, WDS, MC, JF and KR) contributed to study design. JKL and KR selected the clinical study from the larger Janssen clinical trial portfolio for analysis. JKL, MC, TC, WDS and KR contributed to acquisition of data. TC and MC created the data models for the analysis, while all authors ((JKL, RA, TC, WDS, MC, JF and KR) contributed to the analysis and interpretation of data. All authors ((JKL, RA, TC, WDS, MC, JF and KR) were involved in drafting the article or revising it critically for important intellectual content, and all authors (JKL, RA, TC, WDS, MC, JF and KR) approved the final version to be published. JL is the guarantor and accepts full responsibility for the work.

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Competing interests JKL is an employeed of Janssen Pharmaceuticals and a member of the faculty at Delft University of Technology. RA is an employee of Environmental Resource Management. MC is an employee of Environmental Resource Management. TC is an employee of Environmental Resource Management. WDS is an employee of Janssen Pharmaceuticals, NV, a subsidiary of Janssen Pharmaceuticals. JF is a faculty member at Delft University of Technology. KR is an employee of Janssen Pharmaceuticals, NV, a subsidiary of Janssen Pharmaceuticals.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval While participants and the public were involved in the TMC114FD1HTX1002 clinical study (ClinicalTrials.gov: NCT04208061), the LCA was performed as an independent postmortem analysis after the clinical study was completed. None of the participating trial subjects were involved specifically in the LCA analysis nor was any personal identifying information from the trial subjects collected or shared. The underlying clinical study was performed in accordance with the Declaration of Helsinki and Guidelines for Good Pharmacoepidemiology Practice. All participating investigators were required to obtain full governing board approval for conducting non-interventional research involving humans with a limited dataset. Sponsor approval and continuing review were obtained through a central Institutional Review Board (IRB), the New England Independent Review Board (no. 120160939). For academic investigative sites that did not receive authorisation to use the central IRB, full board approval was obtained from their respective governing IRBs, and documentation of approval was submitted to Janssen Research and Development before the site's participation and initiation of any study procedures. All registry participants provided written informed consent and authorisation before participating.

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ORCID iD

Jason Keith LaRoche http://orcid.org/0009-0002-3162-5735

REFERENCES

1 International Standards Organization (ISO). ISO 14040/44: environmental management – life cycle assessment – requirements and guidelines. Geneva International Organization for Standardization; 2006b. Available: https://www.iso.org/standard/37456.html. https://www.iso.org/standard/38498.html
2 Guinée J. *Handbook on life cycle assessment operational guide to the ISO standards. I: LCA in perspective. IIa: guide. IIb: operational annex. III: scientific background*. Dordrecht: Kluwer Academic Publishers, 2002.
3 LCI. 2021. Available: https://www.lifecycleinitiative.org/resources/life-cycle-terminology-2/
4 Association of british pharmaceutical industry (ABPI)/Carbon trust – blister pack carbon evaluation tool, version 1.2;
5 Ecoinvent database V3.8. n.d. Available: https://ecoinvent.org/the-ecoinvent-database/data-releases/ecoinvent-3-8/
6 LaRoche J. Climate footprint of industry-sponsored clinical research: an analysis of a phase-1 randomized clinical study and discussion of opportunities to reduce its impact [Forthcoming]. Dryad; 2023. Available: https://doi.org/10.5061/dryad.12jm63z3q
7 SD Worx. More than 20 % of Europeans commute at least 90 minutes daily. 2018. Available: https://www.sdworx.com/en-en/about-sd-worx/press/2018-09-20-more-20-europeans-commute-least-90-minutes-daily
8 Eurostat. Passenger mobility statistics. 2021. Available: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Passenger_mobility_statistics#Travel_mode
9 Intergovernmental Panel on Climate Change (IPCC). Sixth assessment report – AR6. n.d. Available: https://www.ipcc.ch/assessment-report/ar6/
10 United States Environmental Protection Agency. Greenhouse gas equivalencies calculator. n.d. Available: https://www.epa.gov/energy/greenhouse-gas-equivalencies-calculator
11 De Soete W, Dewulf J, Cappuyns P, *et al*. Exergetic sustainability assessment of batch versus continuous wet granulation based pharmaceutical tablet manufacturing: a cohesive analysis at three different levels. *Green Chem* 2013;15:3039.
12 De Soete W, Boone L, Willemse F, *et al*. Environmental resource footprinting of drug manufacturing: effects of scale-up and tablet dosage. *Resour Conserv Recycl* 2014;91:82–8.
13 Renteria Gamiz AG, De Soete W, Heirman B, *et al*. Environmental sustainability assessment of the manufacturing process of a biological active pharmaceutical ingredient. *J Chem Technol Biotechnol* 2019;94:1937–44.
14 Van der Vorst G, Aelterman W, De Witte B, *et al*. Reduced resource consumption through three generations of galantamine·HBr synthesis. *Green Chem* 2013;15:744.
15 De Soete W, Jiménez-González C, Dahlin P, *et al*. Challenges and recommendations for environmental Sustainability assessments of pharmaceutical products in the healthcare sector. *Green Chem* 2017;19:3493–509.
16 Debaveye S, De Soete W, De Meester S, *et al*. Human health benefits and burdens of a pharmaceutical treatment: discussion of a conceptual integrated approach. *Environ Res* 2016;144:19–31.
17 Penny T, Collins M, Whiting A, *et al*. Care pathways: guidance on appraising sustainability. In: *Coalition for sustainable pharmaceuticals and medical devices (CSPM)*. 2015.
18 UK National Health Services. Delivering a "Net Zero" national health service. n.d. Available: https://www.england.nhs.uk/greenernhs/a-net-zero-nhs/
19 Billiones R. Carbon footprint of clinical trials: a high-level literature review. *Medical Writing* 2022;31.
20 Lyle K, Dent L, Bailey S, *et al*. Carbon cost of pragmatic randomised controlled trials: retrospective analysis of sample of trials. *BMJ* 2009;339:b4187.
21 Borno HT, Zhang L, Siegel A, *et al*. At what cost to clinical trial enrollment? A retrospective study of patient travel burden in cancer clinical trials. *Oncologist* 2018;23:1242–9.
22 LabCorp. A clinical development paradigm to improve patient engagement. 2020. Available: https://drugdevelopment.labcorp.com/content/dam/covance/assetLibrary/whitepapers/Understanding-New-Paradigm-WPDCT001.pdf
23 Burnett J, Clarke M, Darbyshire J, *et al*. Towards sustainable clinical trials. *BMJ* 2007;334:671–3.
24 Subaiya S, Hogg E, Roberts I. Reducing the environmental impact of trials: a comparison of the carbon footprint of the CRASH-1 and CRASH-2 clinical trials. *Trials* 2011;12:31.
25 Seidler EM, Keshaviah A, Brown C, *et al*. Geographic distribution of clinical trials may lead to inequities in access. *Clin Invest* 2014;4:373–80.

26 Alper J, Khandekar E, Shore C. *Virtual clinical trials: challenges and opportunities: proceedings of a workshop (2019)*, ISBN 978-0-309-49488-5. The National Academies of Sciences, Engineering, and Medicine, n.d: 66.
27 Walmart Corporate Newsroom. Automation is reshaping work across America. A new report explores the impact and how communities might respond. 2019. Available: https://corporate.walmart.com/newsroom/2019/02/13/automation-is-reshaping-work-across-america-a-new-report-explores-the-impact-and-how-communities-might-respond#:~:text=Ninety%20percent%20of%20Americans%20live%20within%2010%20miles%20of%20a%20Walmart%20store.&text=knowledge%20of%20human%20capital%20development,Walmart%20Giving's%20Retail%20Opportunity%20Program
28 Horowitz B. Walmart trademarks signal the launch of a new clinical trial business. Insider Intelligence; 2022. Available: https://jnj-my.sharepoint.com/personal/jlaroche_its_jnj_com/Documents/JCI/Sustainability/Walmart%20trademarks%20signal%20the%20launch%20of%20a%20clinical%20trial%20business
29 Purohit A, Smith J, Hibble A. Does telemedicine reduce the carbon footprint of healthcare? A systematic review. *Future Healthc J* 2021;8:e85–91.
30 Ong D, Moors T, Sivaraman V. Complete life-cycle assessment of the energy/Co2 costs of videoconferencing vs face-to-face meetings. In: *IEEE online conference on green communications (GreenCom)*. 2012.
31 Apple. iPhone 8 environmental report. 2017. Available: https://www.apple.com/environment/pdf/products/iphone/iPhone_8_PER_sept2017.pdf
32 Health Care Without Harm, Arup. Health care's climate footprint, green paper number one. 2019. Available: https://noharm-global.org/sites/default/files/documents-files/5961/HealthCaresClimateFootprint_092319.pdf
33 Johnson & Johnson. *5 ways Johnson & Johnson is working to improve the well-being of the world by 2025*. 2021. Available: https://www.jnj.com/latest-news/johnson-johnson-plans-to-improve-global-health-by-2025
34 Smite D, Moe NB, Hildrum J, *et al*. Work-from-home is here to stay: call for flexibility in post-pandemic work policies. *J Syst Softw* 2023;195:111552.
35 Rietmann N, Hügler B, Lieven T. Forecasting the trajectory of electric vehicle sales and the consequences for worldwide Co2 emissions. *J Clean Prod* 2020;261:121038.
36 Kachwala M, Kilgore C, Kinscher K, *et al*. Clinical supply chains: how to boost excellence and innovation. McKinsey & Company Life Sciences Our Insights; 2021. Available: https://www.mckinsey.com/industries/life-sciences/our-insights/clinical-supply-chains-how-to-boost-excellence-and-innovation